CHILDHOOD NEPHROTIC SYNDROME AND STEROID RESPONSIVENESS – A SINGLE CENTER STUDY IN SOUTH INDIA

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CERTIFICATE

This is a bonafide dissertation work entitled **"CHILDHOOD NEPHROTIC SYNDROME AND STEROID RESPONSIVENES – A SINGLE CENTER STUDY IN SOUTH INDIA"** submitted by **KUMARAN.N** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of **MASTER OF PHARMACY** in **PHARMACY PRACTICE** at K.M. College of Pharmacy, Madurai – 625107. It is a bonafide work carried out by him under my guidance and supervision during the year 2011-2012. This dissertation partially or fully has not been submitted for any other degree or Diploma of this University.

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INTRODUCTION[1-14]

BACKGROUND

Pediatric nephrotic syndrome, also known as nephrosis, is defined by the presence of nephrotic-range proteinuria, edema, hyperlipidemia, and hypoalbuminemia. Nephrotic-range proteinuria in adults is characterized by protein excretion of 3.5 g or more per day. However, because of the great range of body sizes in children, the pediatric definition of nephrotic-range proteinuria is more cumbersome.

Nephrotic-range proteinuria in children is protein excretion of more than 40 $mg/m^2/h$. Because 24-hour urine collections are potentially unreliable and burdensome, especially in young children, many pediatric nephrologists instead rely on a single, first-morning urine sample to quantify protein excretion by the ratio of protein to creatinine.

The use of a first-morning urine sample eliminates the contribution of potentially nonpathological orthostatic proteinuria, which might otherwise falsely elevate the protein level in a urine sample collected while a patient is active during the day. A urine protein/creatinine value of more than 2-3 mg/mg indicates nephrotic range proteinuria and correlates with results from 24-hour urine collection.

Kidneys affected by nephrotic syndrome have small pores in the podocytes, large enough to permit proteinuria (and subsequently hypoalbuminemia, because some of the protein albumin has gone from the blood to the urine) but not large enough to allow cells through (hence no hematuria). By contrast, in nephrotic syndrome, RBCs pass through the pores, causing hematuria.

CAUSES

Nephrotic syndrome has many causes and may either be the result of a disease limited to the kidney, called primary nephrotic syndrome, or a condition that affects the kidney and other parts of the body, called secondary nephrotic syndrome.

PRIMARY

Primary causes of nephrotic syndrome are usually described by the histology, i.e. minimal change disease (MCD) like minimal change nephropathy which is the most common cause of nephrotic syndrome in children, focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) like membranous glomerulonephritis which is the main cause of nephrotic syndrome in adult.

They are considered to be "diagnoses of exclusion", i.e. they are diagnosed only after secondary causes have been excluded.

SECONDARY

Secondary causes of nephrotic syndrome have the same histologic patterns as the primary causes, though may exhibit some differences suggesting a secondary cause, such as inclusion bodies.

They are usually described by the underlying cause.

SECONDARY CAUSES BY HISTOLOGICAL PATTERN

Membranous nephropathy (MN):

- Hepatitis B& Hepatitis C
- Sjögren's syndrome
- Systemic lupus erythematosus(SLE)
- Diabetes mellitus
- Sarcoidosis
- Drugs (such as corticosteroids, gold, intravenous heroin)
- Malignancy (cancer)
- Bacterial infections, e.g. leprosy & syphilis
- Protozoal infections, e.g. malaria

Focal segmental glomerulosclerosis (FSGS)

- Hypertensive nephrosclerosis
- HIV
- Obesity
- Kidney loss

Minimal change disease (MCD)

- Drugs, especially NSAIDs in the elderly
- Malignancy, especially Hodgkin's lymphoma
- Leukemia

Drugs that can cause secondary nephrotic syndrome include the following:

- Penicillamine
- Gold
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Interferon
- Mercury
- Heroin
- Pamidronate
- Lithium
-

EPIDEMIOLOGY

The incidence of nephrotic syndrome (NS) is estimated to be in 2–7 cases per 100 000 children per year and its cumulative prevalence rate is 16 per 100 000 children below age of 16. NS is 15 times more common in children than adults. Approximately 90% of children with NS have idiopathic NS (INS), and the remaining 10% have secondary NS, related to infections, systemic diseases, malignancy, and other glomerular diseases. Minimal change nephrotic syndrome (MCNS) accounts for 85% of INS, and more than 95% of these respond to steroid therapy and don't need renal biopsy. Children with steroid-sensitive NS (SSNS), have a benign prognosiswith good preservation of long-term kidney function. Steroid resistance is associated with a high risk of developing chronic kidney disease. Focal segmental glomerulosclerosis (FSGS) is the main cause of steroid resistant NS (SRNS) and accounts for 10%–20% of end-stage renal disease (ESRD) in children. Previous studies emphasize the considerable influence of racial and geographical factors on steroid response and

histological pattern and outcome of INS. Moreover, there are some reports indicating the changing face of childhoodINS with time. Recent studies show that the frequency of FSGS in children has dramatically increased over the past two decades in some parts of world.

In India 20 cases per million are affected by nephrotic syndrome. The ISKDC found that 76.6% of children with INS had MCNS on kidney biopsy findings, with 7% of cases associated with FSGS on biopsy findings.

RACE, SEX, AND AGE-RELATED DEMOGRAPHICS

Black and Hispanic children appear to have an increased risk of steroid-resistant nephrotic syndrome and FSGS.An increased incidence of INS is reported in Asian children, (6 times the rate seen in European children). An increased incidence of INS is also seen in Indian, Japanese, and Southwest Asian children.

Primary, SSNS is rare in Africa, where nephrotic syndrome is more likely to be secondary or steroid-resistant. These variations in ethnic and geographic distribution of INS underscore the genetic and environmental influences in the development of PNS.

In children younger than 8 years at onset, the ratio of males to females varies from 2:1 to 3:2 in various studies. In older children, adolescents, and adults, the male-to-female prevalence is approximately equal. ISKDC data indicate that 66% of patients with either MCNS or FSGS are male, whereas 65% of individuals with MPGN are female.

Of patients with MCNS, 70% are younger than 5 years. Only 20-30% of adolescents with INS have MCNS on biopsy findings. In the first year of life, genetic forms of INS and secondary nephrotic syndrome due to congenital infection predominate.

PROGNOSIS

Since the introduction of corticosteroids, the overall mortality of INS has decreased dramatically from over 50% to approximately 2-5%. Despite the improvement in survival, INS is usually a chronic, relapsing disease and most patients experience some degree of morbidity, including the following:

- Hospitalization, in some instances
- Frequent monitoring both by parents and by physician
- Administration of medications associated with significant adverse events
- A high rate of recurrence (relapses in >60% of patients)
- The potential for progression to chronic kidney failure and end-stage kidney failure (ESKD)

Additionally, INS is associated with an increased risk of multiple complications, including edema, infection, thrombosis, hyperlipidemia, acute kidney failure, and possible increased risk of cardiovascular disease. The prognosis varies, depending on whether the nephrotic syndrome is steroid responsive or steroid resistant.

STEROID-RESPONSIVE NEPHROTIC SYNDROME

Patients who remain responsive to steroids with remission of proteinuria, even with frequent relapses, generally have a good prognosis. The ISKDC found that in 93% of children with INS who responded to steroids, kidney biopsy revealed MCNS. In contrast, 75% of patients who did not initially respond to steroids had histology other than MCNS.

About 90% of children with MCNS (but only 20% of children with focal segmental glomerulosclerosis [FSGS]) achieve remission after the initial course of steroid treatment.

Despite the generally favorable prognosis in patients who respond to steroids, the ISKDC reported a 60% rate of subsequent relapses, which can lead to complications, increased morbidity, and decreased quality of life.A longer course of initial steroid treatment (12 wk rather than the original ISKDC protocol of 8 wk) may reduce the rate of subsequent relapse to 36%,which still represents a large number of patients who undergo repeated courses of immunosuppression, with possible hospitalizations, edema, infections, medication side effects, and other comorbidities.

A long-term study of 398 children with INS found that the percentage of children who became free of relapses during the course of their disease rose from 44% one year after diagnosis to 69% at 5 years and 84% 10 years after diagnosis.Although most children with INS who respond to steroids achieve long-term remission, relapses may continue into adulthood.

Older studies suggested that more than 90% of children achieve long-term remission without further relapses by puberty. However, this has recently been challenged by surveys indicating a rate of relapse during adulthood as high as 27-42%.

In a retrospective study, Vivarelli et al reported that the length of time between initiation of steroid treatment and syndrome remission is an early prognostic indicator for children with INS.In study patients who did not suffer relapse or who relapsed infrequently, the median time from treatment onset to remission was less than 7 days. In patients who had frequent relapses or who developed steroid-dependent nephrotic syndrome, the median time to remission was more than 7 days.

STEROID-RESISTANT NEPHROTIC SYNDROME

Approximately 10% of patients overall with INS do not respond to an initial trial of steroids (2% of patients with MCNS do not respond to steroids). Additionally, about 1-3% of patients who initially do respond to steroids later become resistant to treatment ("late non-responders").

Most patients who do not achieve remission of proteinuria with steroids have kidney biopsy findings other than MCNS. The most common diagnosis in these patients is FSGS.

More than 60% of patients with nephrotic syndrome and FSGS who fail to achieve remission with any treatment progress to end-stage kidney disease (ESKD). In contrast, only 15% progression to ESKD is observed in patients with FSGS who achieve remission by any treatment.Gipson et al reported a 90% lower risk of progression to ESKD in patients with INS who achieved remission.

Thus, patients with steroid-resistant INS have a good prognosis if remission of proteinuria can be achieved by other medications. Failure to respond to treatment (ie, failure to achieve remission) and kidney insufficiency at presentation are predictors of poor outcome and progression to ESKD.

PATHOPHYSIOLOGY

PROTEINURIA AND HYPOALBUMINEMIA

The hallmark of INS is massive proteinuria, leading to decreased circulating albumin levels. The initiating event that produces proteinuria remains unknown. INS is believed to have an immune pathogenesis. Studies have shown abnormal regulation of T-cell subsets and expression of a circulating glomerular permeability factor.

Evidence of the immune-mediated nature of INS is demonstrated by the fact that immunosuppressive agents, such as corticosteroids and alkylating agents, can result in remission of nephrotic syndrome. Furthermore, nephrotic syndrome has been known to remit during infection with the measles virus, which suppresses cell-mediated immunity. However, the precise nature of the immune pathogenic process has yet to be defined.

A circulating factor may play a role in the development of proteinuria in INS. This can be demonstrated by the rapid development of proteinuria in recurrence of nephrotic syndrome after kidney transplantation, the improvement in nephrotic syndrome in such patients after treatment with plasmapheresis, and the experimental induction of proteinuria in animals by plasma from patients with INS.

The nature of this circulating factor is not known. Various cytokines and molecules have been implicated, including the following:

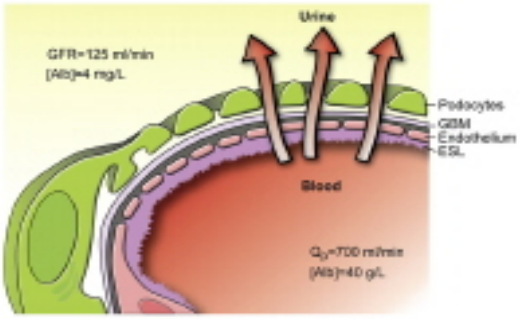
- Interleukin (IL)-2, IL-4, IL-12, IL-13, IL-15, IL-18
- IL-2 receptor
- Interferon-γ
- Tumor growth factor (TGF)-β
- Vascular permeability factor
- Nuclear factor (NF)-κB
- Tumor necrosis factor (TNF)-α

The association of allergic responses with nephrotic syndrome also illustrates the role of the immune system in INS. Nephrotic syndrome has been reported to occur after allergic reactions to bee stings, fungi, poison ivy, ragweed, house dust, jellyfish stings and cat fur. Food allergy might play a role in relapses of INS; a reduced-antigenic diet was associated with improved proteinuria and complete remission in one study.

Additionally, INS is 3-4 times more likely in children with human leukocyte antigen (HLA)-DR7. Steroid sensitive INS has also been associated with HLA-B8 and the *DQB1* gene of HAL-DQW2. A greater incidence of INS is also observed in children with atopy and HLA-B12.

Perhaps the most exciting development in recent years in understanding the pathophysiology of nephrotic syndrome has occurred in the area of podocyte biology.

FIGURE NO: 1 SCHEMATIC DRAWING OF THE GLOMERULAR BARRIER



Podo = podocytes; GBM = glomerular basement membrane; Endo = fenestrated endothelial cells; ESL = endothelial cell surface layer (often referred to as the glycocalyx). Primary urine is formed through the filtration of plasma fluid across the glomerular barrier (arrows); in humans, the glomerular filtration rate (GFR) is 125 mL/min. The plasma flow rate (Qp) is close to 700 mL/min, with the filtration fraction being 20%. The concentration of albumin in serum is 40 g/L, while the estimated concentration of albumin in primary urine is 4 mg/L, or 0.1% of its concentration in plasma.

The glomerular filtration barrier consists of the fenestrated capillary endothelium, the extracellular basement membrane, and the intercalated podocyte foot processes, connected by 35-45 nm slit diaphragms. Nephrotic syndrome is associated with the biopsy finding of fusion (effacement) of podocyte foot processes. This effacement of the podocytes long was thought to be a secondary phenomenon of nephrotic syndrome.

However, theories have shifted toward the podocyte as playing a primary role in the development of proteinuria. The understanding of the pathophysiology of proteinuria in renal diseases has greatly expanded with insights into the molecular biology of the podocyte. Various forms of INS have been described with mutations in podocyte genes, such as those associated with the following:

- Slit-diaphragm and podocyte cytoskeleton -*NPHS1NPHS2, TRCP6, CD2AP, ACTN4*

- Glomerular basement membrane -*LAMB2*
- Mitochondria -*COQ2*
- Transcription factors -*WT1, LMX1B*

Nephrin is a transmembrane protein that is a major structural element of the slit diaphragm and is encoded by the *NPHS1* gene on chromosome 19. Mutations in the *NPHS1* gene are responsible for autosomal recessive, congenital nephrotic syndrome of the Finnish type (FNS).

FNS is characterized by massive proteinuria in the first year of life (usually within the first 3 month) and progression to end-stage kidney disease within the first decade of life, although milder forms of the disease have been described. Mutations in *NPHS1* are usually associated with congenital nephrotic syndrome, but Philipe and colleagues have described *NPHS1* mutations in children aged 6 months to 8 years with later-onset SRNS. Santin has described *NPHS1* mutations in patients with later childhood onset as well as adult-onset SRNS.

Podocin is another podocyte protein that interacts with nephrin and CD2AP and is integral to the assembly of the slit diaphragm. Podocin is encoded by the *NPHS2* gene on chromosome 1. Mutations in the *NPHS2* gene were originally described in patients with autosomal recessive, steroid-resistant INS with FSGS on biopsy. Podocin mutations account for approximately 45-55% of familial and 8-20% of sporadic cases of SRNS.

α-Actinin-4, encoded by the gene *ACTN4* on chromosome 19, cross-links actin filaments of the podocyte cytoskeleton and anchors them to the glomerular basement membrane. The *TRPC6* gene on chromosome 11 encodes for a calcium channel associated with the slit diaphragm. Disruptions in either *ACTN4* or *TRPC6* are associated with autosomal dominant forms of FSGS.

CD2AP, which codes for a podocyte protein that associates with podocin and nephrin, has been associated with the development of nephrotic syndrome in animal models. However, the role it plays in human nephrotic syndrome is unclear. Various case reports have demonstrated heterozygous mutations in *CD2AP* in patients with

nephrotic syndrome and FSGS. One report describes a single patient with a homozygous mutation in *CD2AP* and early onset of nephrotic syndrome with FSGS and diffuse mesangial sclerosis.

Nonmuscle myosin heavy chain 9 (MYH9) is a podocyte protein that binds to the podocyte actin cytoskeleton to perform intracellular motor functions. *MYH9* polymorphisms are estimated to account for more than 40% of end-stage kidney disease cases among blacks and has been associated with FSGS, HIV-associated nephropathy, and focal global glomerulosclerosis (which had been previously attributed to hypertensive nephrosclerosis in many patients). The E1 haplotype of MYH9 is present in 60% of blacks compared with 4% of individuals with European ancestry.

Other genetic forms of nephrotic syndrome continue to shed light on the pathogenesis of INS. Mutations in the developmental regulatory gene *WT1* are associated with forms of congenital nephrotic syndrome associated with male pseudohermaphroditism, Wilms tumor (Denys-Drash syndrome), and gonadoblastoma (Frasier syndrome).

Mutations in phospholipase C epsilon 1 (*PLCE1*), a cytoplasmic enzyme required for podocyte maturation, have been associated with as many as 28% of cases of congenital nephrotic syndrome due to isolated (nonsyndromic) diffuse mesangial sclerosis. Nail-patella syndrome, a disorder characterized by skeletal and nail dysplasia as well as nephrotic syndrome, is caused by mutations in the *LMX1B* gene, which regulates expression of type IV collagen and the podocyte proteins nephrin, podocin, and CD2AP.

Pierson syndrome, characterized by microcoria, abnormal lens shape, cataracts, blindness, severe neurological deficits, congenital nephrotic syndrome and progressive kidney failure, is caused by a mutation in the *LAMB2* gene that codes for laminin b2, which is found in glomerular basement membrane, retina, lens and neuromuscular synapses.

The role of alterations in the slit diaphragm in MCNS has not been elucidated. Podocin appears to be expressed normally in MCNS but decreased in FSGS. Mutations in nephrin and podocin do not at this time appear to play a role in steroid-sensitive nephrotic syndrome. However, acquired alterations in slit diaphragm architecture might play a role in INS apart from actual mutations in the genes encoding podocyte proteins. Various authors have reported changes in expression and distribution of nephrin in MCNS.

Coward et al demonstrated that nephrotic plasma induces translocation of the slit diaphragm proteins nephrin, podocin, and CD2AP away from the plasma membrane into the cytoplasm of the podocyte. These authors also demonstrated the normal plasma might contain factors that maintain the integrity of slit diaphragm architecture and that the lack of certain factors (rather than the presence of an abnormal circulating factor) might be responsible for alterations in the podocyte architecture and development of INS.

Apart from the podocyte and slit diaphragm, alterations in the glomerular basement membrane also likely play a role in the proteinuria of nephrotic syndrome. In INS, the glomerular capillary permeability to albumin is selectively increased, and this increase in filtered load overcomes the modest ability of the tubules to reabsorb protein.

In its normal state, the glomerular basement membrane is negatively charged because of the presence of various polyanions along this surface, such as heparan sulfate, chondroitin sulfate, and sialic acid. This negative charge acts as a deterrent to filtration of negatively charged proteins, such as albumin. Experimental models in which the negative charges are removed from the basement membrane show an increase in albuminuria. Children with MCNS have been reported to have decreased anionic charges in the glomerular basement membrane.

EDEMA

The classical explanation for edema formation is a decrease in plasma oncotic pressure, as a consequence of low serum albumin levels, causing an extravasation of plasma water into the interstitial space. The resulting contraction in plasma volume (PV) leads to stimulation of the renin-angiotensin-aldosterone axis and antidiuretic hormone. The resultant retention of sodium and water by the renal tubules contributes to the extension and maintenance of edema.

While the classical model of edema (also known as the "underfill hypothesis") seems logical, certain clinical and experimental observations do not completely support this traditional concept. First, the PV has not always been found to be decreased and, in fact, in most adults, measurements of PV have shown it to be increased. Only in young children with MCNS have most (but not all) studies demonstrated a reduced PV.

Additionally, most studies have failed to document elevated levels of renin, angiotensin, or aldosterone, even during times of avid sodium retention. Active sodium reabsorption also continues despite actions that should suppress renin effects (eg, as albumin infusion or angiotensin-converting enzyme [ACE] inhibitor administration).

Coupled with these discrepancies is the fact that, in the steroid-responsive nephrotic, diuresis usually begins before plasma albumin has significantly increased and before plasma oncotic pressure has changed. Some investigators have demonstrated a blunted responsiveness to atrial natriuretic peptide (ANP) despite higher-than-normal circulating plasma levels of ANP.

Another model of edema formation, the "overfill hypothesis," postulates a primary defect in renal sodium handling. A primary increase in renal sodium reabsorption leads to net salt and water retention and subsequent hypertension.

ANP might play a role is this mechanism; studies have shown an impaired response to ANP in nephrotic syndrome. This ANP resistance, in part, might be caused by overactive efferent sympathetic nervous activity, as well as enhanced tubular breakdown of cyclic guanosine monophosphate.

Other mechanisms that contribute to a primary increase in renal sodium retention include overactivity of the Na^+ -K^+ -ATPase and renal epithelial sodium channel (RENaC) in the cortical collecting duct and shift of the Na^+/H^+ exchanger NHE3 from the inactive to active pools in the proximal tubule.

A more recent theory of edema formation posits that massive proteinuria leads to tubulointerstitial inflammation and release of local vasoconstrictors and inhibition of vasodilation. This leads to a reduction in single-nephron glomerular filtration rate and sodium and water retention.

Thus, the precise cause of the edema and its persistence is uncertain. A complex interplay of various physiologic factors, such as the following, probably contributes:

- Decreased oncotic pressure
- Increased activity of aldosterone and vasopressin
- Diminished atrial natriuretic hormone
- Activities of various cytokines and physical factors within the vasa recti

HYPERLIPIDEMIA

INS is accompanied by disordered lipid metabolism. Apolipoprotein (apo)-B–containing lipoproteins are elevated, including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoproteins (LDL), and lipoprotein(a), with resultant increases in total cholesterol and LDL-cholesterol. The level of high-density lipoprotein (HDL) cholesterol is normal or low. Elevations in triglyceride levels occur with severe hypoalbuminemia.

The traditional explanation for hyperlipidemia in INS was the increased synthesis of lipoproteins that accompany increased hepatic albumin synthesis due to

hypoalbuminemia. However, serum cholesterol levels have been shown to be independent of albumin synthesis rates.

Decreased plasma oncotic pressure may play a role in increased hepatic lipoprotein synthesis, as demonstrated by the reduction of hyperlipidemia in patients with INS receiving either albumin or dextran infusions. Also contributing to the dyslipidemia of INS are abnormalities in regulatory enzymes, such as lecithin-cholesterol acyltransferase, lipoprotein lipase, and cholesterol ester transfer protein.

THROMBOSIS

Patients with nephrotic syndrome are at increased risk for thrombosis. The incidence rate of thromboembolic complications (TEC) is about 1.8-5% but may be underestimated. One study found the subclinical rate of pulmonary embolism to be 28% using scintigraphic pulmonary ventilation and perfusion studies.Incidence is higher in adults and children with secondary nephrotic syndrome. The incidence is especially high in membranous nephrotic syndrome.

Renal vein thrombosis, deep vein thrombosis, and pulmonary embolism (PE) are the most frequently encountered TEC in children. Other venous sites of thrombosis include the superior sagittal sinus, other cerebral venous sites, and the inferior vena cava.

Arterial thrombosis, although less common than venous TEC, can occur and has been reported at the axillary, subclavian, femoral, coronary, and mesenteric arteries.

Various factors play a role in the increased incidence of thrombosis. Abnormalities described in INS include the following:

- Increased platelet activation and aggregation
- Elevation in levels of factors V, VII, VIII, and XIII and fibrinogen
- Decreased antithrombin III, proteins C and S, and factors XI and XII

- Increased activities of tissue plasminogen activator and plasminogen activator inhibitor-1

These abnormalities in hemostatic factors, combined with potential hypovolemia, immobility, and increased incidence of infection, lead to a hypercoagulable state in INS.

INFECTION

Patients with INS are at increased risk of infection. Peritonitis and sepsis are the most common and serious infections. Peritonitis occurs at a rate of approximately 2-6% and may be accompanied by sepsis or bacteremia. The predominant bacterial causes are *Streptococcus pneumoniae* and Gram-negative enteric organisms such as *Escherichia coli.*

Various infections can also occur, including meningitis, cellulitis, viral infections, and others. Varicella is a particular concern in immunosuppressed patients and can be lethal. Prompt recognition and treatment with acyclovir (or postexposure prophylaxis with varicella-zoster immune globulin [VZIG]) is essential. Routine childhood varicella immunization has alleviated some of the concern regarding this complication.

Infection, viral or bacterial, can trigger relapse of INS and further complicate the course of the condition.

Risk of infection may be increased in INS because of low immunoglobulin (Ig)G levels, which do not appear to be the result of urinary losses. Instead, low IgG levels seem to be the result of impaired synthesis, again pointing to a primary disorder in lymphocyte regulation in INS.

Additionally, increased urinary losses of factor B are noted. This is a cofactor of C3b in the alternative pathway of complement, which plays an important role in the opsonization of encapsulated organisms such as *S pneumoniae.* Impaired T-cell

function may also be present in INS, which contributes to the susceptibility to infection. Finally, the medications used to treat INS, such as corticosteroids and alkylating agents, further suppress the immune system and increase the risk of infection.

ACUTE KIDNEY FAILURE

Acute kidney failure (AKF) is a rare complication of INS, occurring in about 0.8% of cases.Causes include the following:

- Rapid progression of underlying disease (nephrotic syndrome other than MCNS, secondary nephrotic syndrome)
- Bilateral renal vein thrombosis
- Acute interstitial nephritis (AIN) due to drug therapy (eg, antibiotics, nonsteroidal anti-inflammatory agents [NSAIDs], diuretics)
- Acute tubular necrosis (ATN) due to hypovolemia or sepsis

Use of ACE inhibitors or angiotensin II receptor blockers (ARBs) in conjunction with volume depletion can also precipitate AKF.

PHYSICAL EXAMINATION

The most common clinical finding is edema. The edema is pitting and is typically found in the lower extremities, face and periorbital regions, scrotum or labia, and abdomen (ascites). In those children with marked ascites, mechanical restriction to breathing may be present, and the child may manifest compensatory tachypnea. Pulmonary edema and effusions can also cause respiratory distress. Hypertension can be present and is more common in children with FSGS and MPGN rather than MCNS.

Physical findings can also be present due to complications of INS. Abdominal tenderness might indicate peritonitis. Hypotension and signs of shock can be present in children presenting with sepsis. Thrombosis can cause various findings, including tachypnea and respiratory distress (pulmonary thrombosis/embolism), hematuria (renal vein thrombosis), and seizure (cerebral thrombosis).

DIAGNOSTIC CONSIDERATIONS

Acute kidney failure (AKF) is a rare complication of idiopathic nephrotic syndrome. Fever, rash, arthralgia and eosinophilia with a "bland" urinalysis (minimal cellular elements) in the presence of AKF are typical for acute interstitial nephritis. However, obvious clinical symptoms may be absent except for the AKF and unremarkable urinalysis. Gross hematuria, flank pain, and thrombocytopenia may be signs of renal vein thrombosis. Hemoconcentration in the patient with anasarca might indicate intravascular volume depletion.

APPROACH CONSIDERATIONS

The first step in evaluating the child with edema is to establish whether nephrotic syndrome is present, because hypoalbuminemia can occur in the absence of proteinuria (such as from protein-losing enteropathy), and edema can occur in the absence of hypoalbuminemia (eg, in angioedema, capillary leak, venous insufficiency, congestive heart failure).

In order to establish the presence of nephrotic syndrome, laboratory tests should confirm (1) nephrotic-range proteinuria, (2) hypoalbuminemia, and (3) hyperlipidemia. Therefore, initial laboratory testing should include the following:

- Urinalysis
- Urine protein quantification (by first-morning urine protein/creatinine or 24-hour urine protein)
- Serum albumin
- Lipid panel

Once the presence of nephrotic syndrome has been established, the next task is to determine whether the nephrotic syndrome is primary (idiopathic) or secondary to a systemic disorder and, if idiopathic nephrotic syndrome (INS) has been determined, whether signs of chronic kidney disease, kidney insufficiency, or other signs exclude the possibility of MCNS. Therefore, in addition to the above tests, the following should be included in the workup:

- Complete blood count (CBC)

- Metabolic panel (Serum electrolytes, BUN and creatinine, calcium, phosphorus, and ionized calcium levels)
- Testing for HIV, hepatitis B and C
- Complement studies (C3, C4)
- Antinuclear antibody (ANA), anti–double-stranded DNA antibody (in selected patients)

Patients with INS lose vitamin D–binding protein, which can result in low vitamin D levels, and thyroid binding globulin, which can result in low thyroid hormone levels. Consideration should be given, especially in the child with frequently relapsing or steroid-resistant nephrotic syndrome, to testing for 25-OH-vitamin D; 1,25-di(OH)-vitamin D; free T4; and thyroid-stimulating hormone (TSH).

Other tests and procedures in selected patients may include the following:

- Genetic studies
- Kidney ultrasonography
- Chest radiography
- Mantoux test
- Kidney biopsy

Age plays an important role in the diagnostic evaluation of nephrotic syndrome. Children presenting with nephrotic syndrome younger than 1 year of age should be evaluated for congenital/infantile nephrotic syndrome. In addition to the above tests, infants should have the following tests:

- Congenital infection (syphilis, rubella, toxoplasmosis, cytomegalovirus, HIV)
- Kidney biopsy
- Genetic tests for *NPHS1, NPHS2,WT1,* and *LAMB2* mutations as guided by biopsy findings and clinical presentation
- No routine surgical care is indicated for this condition.

Occasionally, a patient with nephrotic syndrome either presents with or develops clinical signs of an acute abdomen, which is frequently due to peritonitis. The diagnosis can usually be made clinically and confirmed by bacteriologic examination of the peritoneal fluid aspirate. The organism most often responsible for

the peritonitis is *Streptococcus pneumoniae*; however, enteric bacteria may also cause peritonitis. Treatment is medical rather than surgical.

URINE STUDIES

Microscopic hematuria is present in 20% of cases of INS and cannot be used to distinguish between minimal change nephrotic syndrome (MCNS) and other forms of glomerular disease.

RBC casts, if present, are suggestive of acute glomerulonephritis, such as postinfectious nephritis, or a nephritic presentation of chronic glomerulonephritis, such as membranoproliferative glomerulonephritis (MPGN). Granular casts may be present and are non-specific to etiology.

The presence of macroscopic (gross) hematuria is unusual in MCNS and suggests another cause, such as MPGN, or a complication of idiopathic nephrotic syndrome (INS), such as renal vein thrombosis.

URINE PROTEIN QUANTIFICATION

First morning urine protein/creatinine is more easily obtained than 24-hour urine studies, is possibly more reliable, and excludes orthostatic proteinuria. A urine protein/creatinine ratio of more than 2-3 mg/mg is consistent with nephrotic-range proteinuria.

A 24-hour urine protein level of more than 40 mg/m^2/h also defines nephrotic-range proteinuria.

BLOOD STUDIES

Serum albumin levels in nephrotic syndrome are generally less than 2.5 g/dL. Values as low as 0.5 g/dL are not uncommon.
Lipid panel findings are typically as follows:

- Elevated total cholesterol, low-density lipoprotein (LDL)-cholesterol
- Elevated triglycerides with severe hypoalbuminemia
- High-density lipoprotein (HDL)-cholesterol (normal or low)

The patient with INS, even MCNS, can present with acute kidney failure due to intravascular volume depletion and/or bilateral renal vein thrombosis. In the absence of the above, elevated BUN and creatinine levels and signs of chronic kidney failure (such as poor growth, anemia, acidosis, hyperkalemia, hyperphosphatemia, elevated parathyroid hormone) suggest a chronic glomerular disease other than MCNS, such as one of the following:

- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy (MN)
- MPGN
- Immunoglobulin (Ig)A nephropathy

Serum sodium levels are low in patients with INS because of hyperlipidemia (pseudohyponatremia), as well as dilution due to water retention. Total calcium levels are low because of hypoalbuminemia, but ionized calcium levels are normal.

On the CBC, an increased hemoglobin and hematocrit indicate hemoconcentration and intravascular volume depletion. The platelet count is often increased.

HIV infection, hepatitis B, and hepatitis C are important secondary causes of nephrotic syndrome. Consequently, screening for these viruses should be performed in all patients presenting with nephrotic syndrome. Consider checking liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), when screening for liver disease.

Low complement levels (C3, C4) are found in postinfectious nephritis, MPGN, and lupus nephritis.

ANA and anti–double-stranded DNA antibody assays are used to screen for collagen-vascular disease in patients with systemic symptoms (fever, rash, weight

loss, joint pain) or any patient with nephrotic syndrome presenting in later school-age or adolescent years when lupus has a higher incidence.

GENETIC TESTING

WT1 testing is indicated for patients with pseudohermaphroditism, Wilms tumor, gonadoblastoma, and diffuse mesangial sclerosis on biopsy. *NPHS1* testing is indicated in patients with biopsy and clinical findings consistent with Finnish-type nephrotic syndrome Because congenital NS has been reported with mutations in *NPHS2*, analysis of this gene should also be considered. Infants with nephrotic syndrome and neurological or visual disturbances should be considered candidates for *LAMB2* testing (Pierson syndrome).

In patients initially or subsequently unresponsive to steroid treatment, in addition to kidney biopsy, consideration should be given to testing for mutations in podocin (*NPHS2*), *ACTN4* and *TRPC6*.

KIDNEY ULTRASONOGRAPHY

Kidney ultrasonography might help to distinguish between MCNS and other chronic kidney disease, but findings are usually nonspecific. In all cases of nephrotic syndrome, the kidneys are usually enlarged due to tissue edema. Increased echogenicity is usually indicative of chronic kidney disease other than MCNS, in which echogenicity is usually normal. A finding of small kidneys indicates chronic kidney disease other than MCNS and is usually accompanied by elevated serum creatinine levels.

CHEST RADIOGRAPHY

Chest radiography is indicated in the child with respiratory symptoms. Pleural effusions are common, although pulmonary edema is rare.

Chest radiography also should be considered prior to steroid therapy to rule out tuberculosis (TB) infection, especially in the child with positive or previously positive Mantoux test or prior treatment for TB.

MANTOUX TEST

Mantoux test (purified protein derivative [PPD]) should be performed prior to steroid treatment to rule out TB infection.

Mantoux testing can be performed concurrent to starting steroid treatment, as treatment with steroids for 48 hours prior to reading the PPD does not mask a positive result and the risk associated with 2 days of steroids is minimal (if tests results are positive, steroids should be immediately stopped).

In children with a positive PPD, previously positive PPD, or prior treatment for TB, chest radiography should be performed.

KIDNEY BIOPSY

A kidney biopsy is not indicated for first presentation of PNS in the child 1-8 years of age unless the history, physical findings, or laboratory results indicate the possibility of secondary nephrotic syndrome or primary nephrotic syndrome other than MCNS. Kidney biopsy is indicated in patients younger than 1 year when genetic forms of congenital nephrotic syndrome are more common, and in patients older than 8 years, when chronic glomerular diseases such as FSGS have a higher incidence.

In select preadolescent patients older than 8 years, empirical steroid treatment can be considered prior to kidney biopsy, but this should occur only under the care of a pediatric nephrologist experienced with nephrotic syndrome. Some authors have recommended performing a kidney biopsy in patients older than 12 years.

Kidney biopsy should also be performed when history, examination, or laboratory findings indicate secondary nephrotic syndrome or kidney disease other than MCNS. Thus, a kidney biopsy is indicated if patients have any of the following:

- Symptoms of systemic disease (eg, fever, rash, joint pain)
- Laboratory findings indicative of secondary nephrotic syndrome (eg, positive ANA findings, positive anti–double-stranded DNA antibody findings, low complement levels)
- Elevated creatinine levels unresponsive to correction of intravascular volume depletion
- A relevant family history of kidney disease

Finally, in patients who are initially or subsequently unresponsive to steroid treatment, kidney biopsy should be performed, because steroid unresponsiveness has a high correlation with prognostically unfavorable histology findings such as FSGS or MGN.

HISTOLOGIC FINDINGS

If a kidney biopsy is performed, various histologic findings can be present, depending on the etiology of the nephrotic syndrome. Briefly, the most common histological types of INS are as follows.

MINIMAL CHANGE NEPHROTIC SYNDROME

MCNS indicates glomerular morphology that on light microscopic examination is little different from normal. Minimal mesangial hypercellularity may be present. Immunofluorescent microscopy (IF) usually reveals no presence of immune deposits.

Occasionally, mesangial IgM deposition may be seen on IF. Some consider the presence of IgM to indicate a separate entity (IgM nephropathy), whereas others consider this to be a variant of MCNS. The presence of IgM may indicate a more difficult course of nephrotic syndrome, with frequent relapses, steroid dependence, or steroid resistance, although the overall prognosis is still usually favorable. The only significant change seen on electron microscopy (EM) is flattening and fusion of the podocyte foot processes (effacement).

DIFFUSE MESANGIAL PROLIFERATION

Diffuse mesangial proliferation (DMP) refers to increased mesangial matrix and increased mesangial hypercellularity. IF findings are negative and EM reveals the typical foot process effacement of MCNS. Patients with DMP have an increased incidence of steroid resistance, although whether these patients are at increased risk for progression to kidney failure is unclear.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS describes a lesion in which, as seen on LM, discrete segments of the glomerular tuft reveal sclerosis (segmental); some glomeruli are involved, and others are spared (focal).

Adhesion of the glomerular tuft to Bowman capsule (synechiae) is observed. Glomerular hypertrophy is common. Interstitial fibrosis and tubular atrophy are often present and correlate with the severity of disease.

IF reveals IgM and C3 trapped in the sclerotic areas. As in MCNS, EM reveals effacement of the podocyte foot processes. Additionally, EM reveals obliteration of capillary lumens by fine granular and lipid deposits.

A subtype of FSGS, in which the glomerular tufts demonstrate collapse of capillaries (collapsing glomerulopathy) on LM, has a poorer prognosis and high rate of progression to end-stage kidney failure (ESKD).

FSGS is not a specific disease but a histopathological finding that can be associated with INS but can also be found in a wide variety of other conditions, including HIV nephropathy, heroin nephropathy, reflux nephropathy, obstructive uropathy, renal hypoplasia, hypertension, obesity, and Alport syndrome.

As always, clinical and histopathological correlations must always be made when considering the findings evident on kidney biopsy.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is also known as mesangiocapillary glomerulonephritis. Glomeruli are typically lobulated in appearance on LM findings and demonstrate mesangial proliferation. Silver stain may reveal characteristic duplication of the glomerular basement membrane ("tram-track" appearance). IF findings reveal characteristic capillary deposition of C3.

Three types of MPGN are recognized and can be distinguished by electron microscopy findings according to the location of immune deposits. Type 1 is subendothelial; type 2 has ribbonlike, dense intramembranous deposits; and type 3 is subendothelial and subepithelial. Some controversy surrounds the existence of type 3 MPGN as a distinct entity or a variant of type 1.

MEMBRANOUS NEPHROPATHY

MN is a rare finding in INS of childhood, comprising only approximately 1% of biopsies, whereas in adult INS, MN can be found in 25-40% of cases. Light microscopy typically reveals thickening of the glomerular basement membrane. Silver stain may reveal characteristic "spikes," resulting from protrusion of basement membrane around immune deposits. IF reveals fine granular IgG and complement staining along the periphery of the glomerular capillary wall. EM reveals subepithelial electron-dense deposits.

Various staging schemes are recognized for the different histological lesions of INS. In general, when referring to kidney biopsy, the severity and chronicity of the disease is determined by the extent of tubulointerstitial fibrosis. The greater the extent of fibrosis, the greater the irreversibility of the disease and the poorer the prognosis, regardless of histological subtype.

TREATMENT

The various causes in nephrotic syndrome can be treated as follows:

HYPERLIPIDEMIA

Lipid abnormalities generally resolve when nephrotic syndrome is in remission. Dietary modification does not appear to be effective in limiting hyperlipidemia during active nephrotic syndrome.

Chronic hyperlipidemia has been linked to increased risk of atherosclerosis and coronary artery disease. Chronic hyperlipidemia has also been associated with progression of renal disease. However, the small studies to date of lipid-lowering agents in pediatric INS have not shown an improvement in proteinuria or progression of renal disease.

Dyslipidemias in adults with nephrotic syndrome have been successfully treated with the following:

- Statins (simvastatin, lovastatin)
- Fibrates (gemfibrozil)
- Bile-acid binding resins (cholestyramine)
- Probucol

Children with INS have been effectively treated with probucol, but this agent has been associated with prolonged QT interval and is not available in the United States. Gemfibrozil has also been shown to be effective in childhood nephrotic syndrome in small studies.

Small studies have shown that simvastatin and lovastatin are well tolerated and effective in childhood INS. Total cholesterol, triglycerides, and LDL cholesterol were reduced by 42%, 44%, and 46%, respectively. No changes in proteinuria, hypoalbuminemia, or progression of renal disease were noted.

In order to monitor for treatment-associated rhabdomyolysis, children treated with statins should have creatine kinase measured prior to initiating therapy and every 6-12 weeks during treatment. Patients and families should be instructed to report muscle soreness, tenderness, or pain. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels should be measured before initiating treatment and about every 3 months thereafter to monitor for liver toxicity.

Long-term safety studies regarding statins in pediatrics are lacking, and routine use of statins were not recommended by an expert panel in 2004. The only drugs recommended at this time by the panel were bile acid sequestrants.

THROMBOEMBOLISM

Initial treatment of thromboembolic complications includes thrombolysis with anticoagulants (such as heparin) and/or fibrinolytic agents (ie, tissue plasminogen activator, streptokinase, urokinase). For secondary prevention, warfarin is often prescribed for a period of as long as 6 months.

Empiric prophylactic anticoagulation is not routinely indicated in INS. Some practitioners advocate the use of long-term, low-dose aspirin in patients with chronic nephrotic syndrome (eg, frequently relapsing nephrotic syndrome, SDNS, SRNS). However, adequate controlled trials examining the use of aspirin have not been performed.

ACUTE KIDNEY FAILURE

Acute kidney failure may rarely result from complications of INS, from the underlying disease, or from drug therapy. In most cases, acute kidney failure is reversible with remission of nephrotic syndrome, correction of intravascular volume contraction, and/or (in patients with acute interstitial nephritis) removal of inciting agent.

CORTICOSTEROID THERAPY

The original International Study of Kidney Disease in Children (ISKDC) protocol recommended induction therapy with oral prednisone or prednisolone at 60 $mg/m^2/d$ (2 mg/kg/d), with a maximum of 60 mg, daily for 4 weeks. Traditionally, the total daily dose was split into two doses. However, a single daily dose of steroids has efficacy equal to split dosing and fewer side effects.

Subsequent studies have shown that a longer period of initial steroid treatment (6 weeks rather than 4 weeks) reduces the subsequent rate of relapse. Thus, the general consensus now is to prescribe the initial daily steroids for 6 weeks.

Original guidelines recommended that induction therapy be followed with maintenance therapy with oral prednisone or prednisolone at 40 mg/m^2 (or 1.5 mg/kg), with a maximum of 40 mg, given as a single dose on alternate days for 4 weeks. Subsequent studies demonstrated that a longer alternate-day maintenance period of 6 weeks resulted in a lower rate of relapse.

Thus, the general consensus now is daily induction steroid treatment for 6 weeks, followed by alternate-day maintenance therapy for another 6 weeks. After 6 weeks of alternate day treatment, steroids may be stopped or slowly tapered over a variable length of time.

Longer duration of alternate-day steroid treatment may further reduce the number of children with subsequent relapses. A meta-analysis concluded that, after the initial daily steroid induction phase, continuation of alternate day steroids for 6 months could reduce the subsequent relapse rate by 33% compared with shorter alternate-day treatment. No adverse effects were noted with the longer steroid treatment, although the authors cautioned the adequate randomized controlled trials comparing shorter versus long-term alternate day steroid treatment still needed to be conducted.

TREATMENT OF RELAPSES

For infrequent relapses, steroids are resumed, although for a shorter duration than treatment during initial presentation. Prednisone, 2 mg/kg/d (60 $mg/m^2/d$), is given as a single morning dose until the patient has been free of proteinuria for at least 3 days.

Following remission of proteinuria, prednisone is reduced to 1.5 mg/kg (40 mg/m^2) given as a single dose on alternate days for 4 weeks. Steroids may then be stopped or gradually tapered.

DIURETIC THERAPY

Diuretic therapy may be beneficial, particularly in children with symptomatic edema. Loop diuretics, such as furosemide (starting at 1-2 mg/kg/d) may improve edema; their administration, however, should be handled with care because plasma volume contraction may already be present, and hypovolemic shock has been observed with overly aggressive therapy.

Metolazone may be beneficial in combination with furosemide for resistant edema. Patients must be monitored carefully on this regimen. If the child is sent home on diuretic therapy, the family must have clear guidelines about discontinuing therapy when edema is no longer present and careful communication with the family should continue.

When a patient presents with anasarca and signs of intravascular volume depletion (such as a high hematocrit, indicative of hemoconcentration), consideration should be given to administration of 25% albumin, although this is controversial. Rapid administration of albumin can result in pulmonary edema.

The author's practice has been to administer 25% albumin at a dose of 1 g/kg body weight given as a continuous infusion over 24 hours. Intravenous albumin may be particularly useful in diuretic-resistant edema and in patients with significant ascites and/or scrotal, penile or labial edema.

ANTIHYPERTENSIVE THERAPY

Antihypertensive therapy should be given when hypertension is present and particularly if it persists, but caution should be exercised. In some patients, the hypertension will respond to diuretics. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) may also contribute to reducing proteinuria but should be used cautiously in the presence of acute kidney failure or volume depletion because they can worsen kidney function in these settings.

ACE inhibitors and ARBs can cause birth defects, so adolescent women who are taking these agents must be counseled regarding use of birth control, and pregnancy testing should be considered before starting these agents.

Calcium channel blockers and beta-blockers may also be used as first-line agents for hypertension.

FREQUENTLY RELAPSING AND STEROID-DEPENDENT DISEASE

Frequently-relapsing nephrotic syndrome (FRNS) is defined as steroid-sensitive nephrotic syndrome (SSNS) with 2 or more relapses within 6 months or more than 3 relapses within a 12-month period. Steroid-dependent nephrotic syndrome (SDNS) is defined as SSNS with 2 or more consecutive relapses during tapering or within 14 days of stopping steroids.

For FRNS and SDNS, the clinical evidence is inadequate to support a preferred method of treatment. Therefore, practitioners must rely on their clinical experience and discuss the potential advantages and disadvantages of each treatment with families and patients. Given the complexity of management in these cases and the importance of clinical experience, patients should be referred to a pediatric nephrologist if this has not already been done.

ALKYLATING AGENTS

Alkylating agents (eg, cyclophosphamide [CYP], chlorambucil, nitrogen mustard) offer the benefit of possible sustained remission after a defined course of treatment, although with the possible risk of infertility and other side effects (see Side Effects of Drug Therapy).

An increased risk of seizures is noted with chlorambucil. Additionally, a higher incidence of infections and leukopenia may be seen with chlorambucil compared with CYP. Because of these risks, and the need to give nitrogen mustard intravenously, CYP has generally been the preferred alkylating agent.

Steroids (prednisone 2 mg/kg/d in single dose, max 60 mg) are usually started prior to administration of CYP in order to induce remission of proteinuria before starting CYP. After initiation of CYP, if proteinuria remains in remission, prednisone is reduced to 1.5 mg/kg on alternate days for 4 weeks, then slowly tapered over 4 weeks.

CYP (2 mg/kg daily) is given orally for 8-12 weeks. An influential study found that a 12-week course was more effective than an 8-week course in producing sustained remission of nephrotic syndrome. However, a subsequent randomized trial did not reach this same conclusion, and the optimal duration of CYP treatment is still unclear at this time.

Patients must have weekly complete blood counts to monitor for leukopenia. Patients must also maintain adequate hydration and take CYP in the morning (not at bedtime) to limit the risk of hemorrhagic cystitis. Families must be counseled to report gross hematuria, fever, or severe illness.

CALCINEURIN INHIBITORS

Calcineurin inhibitors (eg, cyclosporine A [CSA], tacrolimus [TAC]) are useful steroid-sparing agents. These agents can also be used in those children who fail to respond to, or subsequently relapse after, treatment with CYP, or in children whose families object to the use of CYP.

Calcineurin inhibitors have disadvantages: prolonged courses of treatment are needed, nephrotic syndrome tends to recur when treatment is stopped, and nephrotoxic injury may occur. Consideration should be given to kidney biopsy after prolonged treatment to monitor for calcineurin inhibitor–induced nephrotoxicity and fibrosis.

Limited studies are available regarding the effectiveness of TAC compared with CSA. A single-center study by Choudhry et al in 41 patients with idiopathic SRNS found that TAC (0.1-0.2 mg/kg/d) or CSA (5-6 mg/kg/d) have similar efficacy in inducing remission in patients with idiopathic SRNS at 6 months and 1 year when combined with alternate-day low-dose corticosteroids and enalapril.

Relapse was significantly greater with CSA than with TAC; in addition, TAC decreased blood cholesterol levels to a greater extent and resulted in fewer incidents of nephrotoxicity that necessitated discontinuance than CSA. Cosmetic adverse effects (eg, hypertrichosis, gum hypertrophy) were significantly more frequent with CSA. Thus, TAC therapy is a promising alternative to CSA because of the lower relapse risk and lack of cosmetic adverse effects.

CYCLOSPORINE A

CSA treatment is started at 3-5 mg/kg/d divided every 12 hours; doses are adjusted for trough concentrations of 50–125 ng/mL. However, trough levels correlate poorly with area-under-the-curve (AUC) pharmacokinetics and may not represent true exposure to CSA. levels obtained 2 hours after administration (C2) have better correlation with AUC.

Kidney function and drug levels must be carefully monitored due to the risk of CSA-induced nephrotoxicity.

Low-dose steroids are continued for a variable length of time. As many as 40% of patients may need to remain on steroids during CSA treatment to maintain remission.

TACROLIMUS

TAC is started at a dose of 0.1 mg/kg daily divided every 12 hours and adjusted to keep trough level about 5-10 ng/mL.Our practice is to use the lowest possible dose that sustains remission and to aim for a trough level of around 3-5 ng/mL. TAC trough levels correspond better to AUC than CSA, allowing better determination of dosing and exposure with TAC than with CSA.As with CSA, continuing low-dose steroids is often necessary to maintain remission, although some patients may eventually be able to discontinue steroid treatment.

LEVAMISOLE

Levamisole is an anthelmintic drug that has immune-modulating effects and can be effective in reducing the relapse rate in FRNS. However, it is unavailable in the United States. Side effects include leukopenia, hepatic dysfunction, agranulocytosis, vasculitis, and encephalopathy. Levamisole is prescribed at a dose of 2.5 mg/kg given on alternate days.

MYCOPHENOLATE MOFETIL

Although small studies have shown mycophenolate mofetil (MMF) to be effective in reducing the number of relapses in FRNS and SDNS, adequate randomized controlled trials still need to be performed. One study of 33 patients, using a 6-month course of MMF with tapering dose alternate day steroids, achieved a 75% remission rate, which persisted in 25% of patients after discontinuation of MMF. Additionally, this study demonstrated an improvement in relapse rate from once every 2 months to once every 14.7 months.

Thus, MMF might be a useful steroid-sparing agent in stable patients (without excessive edema, need for hospitalizations and without other serious complications) whose families wish to avoid the possible side effects of CYP, CSA, or TAC. However, response to MMF varies and is less reliable than other treatments.

MMF is started at a dose of 600 mg/m^2 twice daily. Complete blood counts should be monitored for bone marrow suppression, and liver function tests should occasionally be performed to monitor for hepatic toxicity.

STEROID-RESISTANT DISEASE AND FOCAL SEGMENTAL GS

Adequate randomized controlled trials have not yet been reported to give sufficient evidence to guide treatment of steroid-resistant nephrotic syndrome (SRNS).A current National Institutes of Health (NIH)-sponsored, multicenter, randomized clinical trial has recently concluded enrollment and will compare CSA versus MMF for treatment of focal segmental glomerulosclerosis (FSGS).

The most frequently recommended treatment for FSGS and SRNS is CSA. Approximately 36% of children with SRNS may achieve remission with this agent.CSA is dosed as for FRNS and SDNS. However, higher doses and trough levels may be required to achieve remission in SRNS and FSGS.TAC may be effective as well, although studies are limited at this time.Most studies to date have shown no clear benefit to the use of alkylating agents in FSGS and SRNS.

In a nonrandomized study of in children with SRNS, approximately half responded to MMF. Of 34 patients treated with CSA prior to MMF, 20% achieved complete remission, 39% achieved partial remission, and 41% had no response. Among 18 patients treated only with MMF, 27% achieved complete remission, 33% partial remission, and 40% had no response.The MMF regimen used in this study was 500-600 mg/m^2 body surface area/d or 18 mg/kg/d [maximum 1 g] for a minimum of 6 mo.

The histology in these patients consisted of MCNS, FSGS, MPGN, crescentic glomerulonephritis, and membranous nephropathy). Further studies are needed on the use of MMF in SRNS and FSGS.

A controversial treatment involves high-dose, intravenous methylprednisolone tapered over 78 weeks, in combination with alternate-day oral prednisone; CYP or chlorambucil is added if remission is not achieved in the first 10 weeks. The authors reported a 52% remission rate in SRNS.However, subsequent studies using this protocol have not duplicated the initial success. The risk of steroid toxicity and infection, as well as lack of sufficient evidence for the effectiveness of this protocol, have dampened enthusiasm for this treatment.

The use of an ACE inhibitor (eg, enalapril), either alone or in combination with an ARB (eg, losartan), has been shown to reduce proteinuria in FSGS/SDNS and should be considered in all patients, even in the absence of hypertension. Accordingly, ACE inhibitors and ARB should be considered as preferred agents in patients with hypertension. ACE inhibitor and ARB treatment may also have a renoprotective effect and slow progression of renal disease by inhibiting pathways of fibrosis.

DIET AND ACTIVITY

Reduce sodium intake to 1000–2000 mg daily. Foods high in sodium include salt used in cooking and at the table, seasoning blends (garlic salt, Adobo, season salt, etc.) canned soups, canned vegetables containing salt, luncheon meats including turkey, ham, bologna, and salami, prepared foods, fast foods, soy sauce, ketchup, and salad dressings. On food labels, compare milligrams of sodium to calories per serving. Sodium should be less than or equal to calories per serving.

Eat a moderate amount of high protein animal food: 3-5 oz per meal (preferably lean cuts of meat, fish, and poultry)

Avoid saturated fats such as butter, cheese, fried foods, fatty cuts of red meat, egg yolks, and poultry skin. Increase unsaturated fat intake, including olive oil, canola oil, peanut butter, avocadoes, fish and nuts. Eat low-fat desserts.

Increase intake of fruits and vegetables. No potassium or phosphorus restriction necessary.

Monitor fluid intake, which includes all fluids and foods that are liquid at room temperature. Fluid management in nephrotic syndrome is tenuous, especially during an acute flare.

A normal activity plan is recommended. Because viral respiratory illnesses are often associated with relapses of nephrotic syndrome, keeping children with INS away from those who have obvious respiratory tract infections may be beneficial. However, children should not be kept out of school and should have as normal a routine as possible.

VACCINATION

Yearly influenza vaccination is recommended to prevent serious illness in the immunocompromised patient, as well as to prevent this possible trigger of relapse.

Pneumococcal vaccination should be administered to all patients with INS upon presentation. Vaccination should be repeated every 5 years while the patient continues to have relapses.

Routine childhood vaccines with live virus strains are contraindicated during steroid therapy and for a minimum of 1 month afterward. Care must be taken in administering live viral vaccines to children in remission from FRNS, who might need to restart steroid therapy shortly after vaccination.

Because of the high risk of varicella infection in the immunocompromised patient, postexposure prophylaxis with varicella-zoster immune globulin is recommended in the nonimmune patient. Patient with varicella-zoster infection should be treated with acyclovir and carefully monitored. Varicella immunization is safe and effective in patients with INS who are in remission and off steroid treatment (with the usual precautions for administering live viral vaccines to patients who have received steroids).

Routine nonlive viral vaccines should be administered according to their recommended schedules. Despite the former belief that routine immunization can trigger relapse of nephrotic syndrome, no solid evidence supports this, and the risk of these preventable childhood illnesses exceeds the theoretical, unproven risk for triggering relapses.

CONSULTATIONS AND LONG-TERM MONITORING

Because of the complexity of care of INS in all but the simplest of cases, the lack of strong clinical evidence supporting treatment options, and the great deal of experience required in successfully managing these patients, care of the patient with INS should always be performed in consultation with a pediatric nephrologist.

In cases that have initially been managed by the primary care specialist, referral to a pediatric nephrologist is mandatory in cases of FRNS, SDNS, SRNS, secondary nephrotic syndrome, and situations in which a kidney biopsy is necessary.

Referral to a pediatric nephrologist is mandatory for all children with nephrotic syndrome whose symptoms fail to respond to initial therapy (complete remission of proteinuria); in most of these patients, a percutaneous renal biopsy is indicated, and an alternative treatment plan may be desirable.

As with all chronic illnesses, many psychosocial issues may need to be addressed, including behavior, adherence to medication, adequate parental/caretaker supervision, medical insurance, missed work and school due to hospitalizations and outpatient visits, and many other important issues. Consultation with social workers and mental health care workers may be useful.

LONG-TERM MONITORING

Ambulatory monitoring of the child's condition and response to treatment is a very important aspect of the overall management of nephrotic syndrome.

Home monitoring of urine protein and fluid status is an important aspect of management. Parents and/or caregivers should be trained to monitor first morning urine proteins at home with urine dipstick. Weight should be checked every morning as well and a home logbook should be kept recording the patient’s daily weight, urine protein, and steroid dose if the child is receiving steroids.

Families and patients are instructed to call for any edema, weight gain, or urine testing 2+ or more for protein for more than 2 days. Rapid detection of relapse of proteinuria by home testing of urine can allow early initiation of steroid treatment before edema and other complications develop. Urine testing at home is also useful in monitoring response (or nonresponse) to steroid treatment.

PATIENT EDUCATION

Soon after nephrotic syndrome is diagnosed, the patient and family should be educated about the disease, its management, and its expected course. The family should participate in therapeutic decisions and should be encouraged to adhere to the medical regimen.

As with all chronic illnesses, many psychosocial issues may need to be addressed, including (but not limited to) the following:

- Behavior
- Adherence to medication
- Adequate parental/caretaker supervision
- Medical insurance
- Missed work and school due to hospitalizations and outpatient visits
- Consultation with social workers and mental health care workers may be useful.

PREDNISOLONE[15-17]

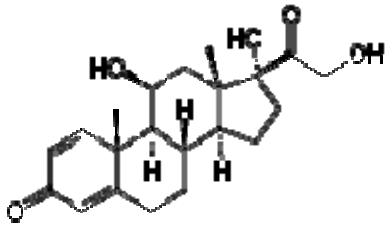
BRAND NAME: WYSOLONE, NUCORT, DELTACORTIL, HOSTACORTIN-H.

IUPAC NAME:(11β) – 11, 17, 21 – trihydroxypregna – 1,4 – diene – 3, 20 – dione.

CHEMICAL FORMULA:$C_{21}H_{28}O_5$

MOLECULAR MASS:360.44 gm/mol

STRUCTURAL FORMULA



DESCRIPTION

Prednisolone is the most commonly-prescribed oral corticosteroid. The drug is metabolized in the liver to its active form, prednisolone. Relative to hydrocortisone, prednisolone is roughly 4 times as potent as a glucocorticoid. Prednisolone is intermediate between hydrocortisone and dexamethasone in duration of action. Prednisolone was first approved by the FDA in 1955.

DOSAGE FORMS: Tablet, Injection.

MECHANISM OF ACTION

Glucocorticoids are naturally occurring hormones that prevent or suppress inflammation and immune responses when administered at pharmacological doses. At a molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately protein synthesis to achieve the steroid's intended action. Such actions may include: inhibition of leukocyte infiltration

at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humoral immune responses. Some of the net effects include reduction in edema or scar tissue, as well as a general suppression in immune response. The degree of clinical effect is normally related to the dose administered. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, collectively called lipocortins. Lipocortins, in turn, control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the precursor molecule arachidonic acid.

Anti-inflammatory and immunosuppressive actions:

- Inhibition of gene transcription for COX-2, cytokines, cell adhesion molecules, and inducible NO synthetase
- Blockage of Vit D3-mediated induction of osteocalcin gene in osteoblasts
- Modification of collegenase gene transcription
- Increase synthesis annexin-1, important in negative feedback on hypothalamus and anterior pituitary gland
- Anti-inflammatory action, it is presumed.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Prednisolone irreversibly binds with glucocorticoid receptors (GR) alpha and beta for which they have a high affinity. AlphaGR and BetaGR are found in virtually all tissues with variable numbers between 3000 and 10000 per cell, depending on the tissue involved. Prednisolone can activate and influence biochemical behaviour of most cells. The steroid/receptor complexes dimerise and interact with cellular DNA in the nucleus, binding to steroid-response elements and modifying gene transcription. They both induce synthesis of some genes and, therefore, some proteins, and inhibit synthesis of others.

PHARMACOKINETICS

Absorption

Prednisolone is rapidly absorbed across the GI membrane following oral administration. Peak effects can be observed after 1—2 hours. The circulating drug binds extensively to the plasma proteins albumin and transcortin, with only the unbound portion of a dose active.

Distribution

Systemic prednisolone is quickly distributed into the kidneys, intestines, skin, liver and muscle. Corticosteroids distribute into the breastmilk and cross the placenta.

Plasma Protein Binding: 90%

Metabolism

Extensively metabolized in the liver.

Elimination

The inactive metabolites, as well as a small portion of unchanged drug, are excreted in the urine.

Half-life: 18 to 36 hours.

Paediatric Dose for Nephrotic Syndrome

Initial (first three episodes): 2 mg/kg/day (maximum 80 mg/day) in divided doses 3 to 4 times/day until urine is protein free for 3 consecutive days (maximum: 28 days); followed by 1 to 1.5 mg/kg/dose given every other day for 4 weeks.

Maintenance dose for frequent relapses: 0.5 to 1 mg/kg/ dose given every other day for 3 to 6 months.

OVERDOSAGE

Long-term/overdose use of high prednisolone doses can lead to symptoms such as thinning skin, easy bruising, changes in the shape or location of body fat (especially in your face, neck, back, and waist), increased acne or facial hair, menstrual problems, impotence, or loss of interest in sex.

ROUTE OF ADMINISTRATION: Oral, intramuscular, intraarticular.

DOSAGE FORM/ STRENGTH: 5, 10, 20, 40 mg tablets.

INDICATIONS AND CLINICAL USE

- acute lymphocytic leukemia
- acute respiratory distress syndrome
- Addison's disease
- adrenal hyperplasia
- adrenocortical insufficiency
- allergic conjunctivitis
- amyloidosis
- angioedema
- ankylosing spondylitis
- anterior segment inflammation
- asthma
- atopic dermatitis
- autoimmune hepatitis
- Behcet's syndrome
- berylliosis
- bone pain
- bursitis
- iritis
- juvenile rheumatoid arthritis
- keratitis
- kidney transplant rejection
- Loeffler's syndrome
- lupus nephritis
- mixed connective tissue disease
- multiple myeloma
- myasthenia gravis
- mycosis fungoides
- nephrotic syndrome
- optic neuritis
- osteoarthritis
- pemphigus
- pericarditis
- pneumonia

- carpal tunnel syndrome
- chorioretinitis
- chronic lymphocytic leukemia
- corneal ulcer
- Crohn's disease
- dermatitis
- dermatomyositis
- endophthalmitis
- epicondylitis
- erythroblastopenia
- gout
- gouty arthritis
- graft-versus-host disease
- headache
- hemolyticanemia
- Hodgkin's disease
- hypercalcemia
- hypoplasticanemia
- idiopathic thrombocytopenic purpura
- pneumonitis
- polyarteritisnodosa
- polychondritis
- polymyositis
- psoriasis
- rheumatic carditis
- rheumatoid arthritis
- sarcoidosis
- severe pain
- Stevens-Johnson syndrome
- systemic lupus erythematosus
- temporal arteritis
- tenosynovitis
- thrombocytopenia
- thyroiditis
- tuberculosis
- ulcerative colitis
- urticaria
- Wegener's granulomatosis

CONTRAINDICATIONS

- abrupt discontinuation
- breast-feeding
- cataracts
- children
- coagulopathy
- Cushing's syndrome
- diabetes mellitus
- diverticulitis
- fungal infection
- GI disease
- glaucoma
- heart failure
- inflammatory bowel disease
- measles
- myasthenia gravis
- myocardial infarction
- osteoporosis
- peptic ulcer disease
- psychosis
- renal disease
- seizure disorder
- surgery
- thromboembolic disease
- tuberculosis

- hepatic disease
- herpes infection
- hypertension
- hypothyroidism
- infection
- ulcerative colitis
- vaccination
- varicella
- viral infection
- visual disturbance

PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

- There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.
- Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
- The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.
- Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.
- Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
- Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis and myasthenia gravis.
- Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

ADVERSE EFFECTS

- A lengthy course of prednisolone can cause bloody or black tarry stools from bleeding into the stomach (this requires urgent medical attention); filling or rounding out of the face; muscle cramps or pain; muscle weakness; nausea; pain in back, hips, ribs, arms, shoulders, or legs; reddish-purple stretch marks on arms, face, legs, trunk, or groin; thin and shiny skin; unusual bruising; urinating at night; rapid weight gain; and wounds that will not heal.
- Prolonged use of prednisolone can lead to the development of osteoporosis which makes bones more fragile and susceptible to fractures. One way to help alleviate this side effect is through the use of calcium and vitamin D supplements.
- Swelling of the pancreas has also been reported.
- Prednisolone can cause increased blood sugar levels for diabetics.
- Other effects include decreased or blurred vision, increased eye pressure, increased thirst, cataract formation, confusion, rare cases of dementia in otherwise-healthy elderly patients, and nervousness.

DRUG-DRUG INTERACTIONS

Many drugs can interact with prednisolone. Below is a list of drugs which shows interaction with prednisolone.

- aspirin (taken on a daily basis or at high doses);
- a diuretic (water pill);
- a blood thinner such as warfarin (Coumadin, Jantoven);
- cyclosporine (Gengraf, Neoral, Sandimmune);
- insulin or diabetes medications you take by mouth;
- ketoconazole (Nizoral);
- rifampin (Rifadin, Rifater, Rifamate, Rimactane); or
- seizure medications such as phenytoin (Dilantin) or phenobarbital (Luminal, Solfoton).

CYCLOPHOSPHAMIDE[15-17]

BRANDNAME:ENDOXAN,CYCLOXAN, NEOSAR, PROCYTOX, REVIMMUNE.

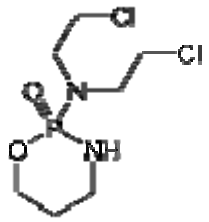
IUPAC NAME:N, N-bis (2-chloroethyl)-1,3,2 oxazaphosphinan-2-amine-2-oxide.

CHEMICAL FORMULA:$C_{17}H_{15}Cl_2N_2O_2P$

MOLECULAR MASS:261.086 gm/mol

PHARMACOLOGICAL CLASSIFICATION: Alkylating agent, nitrogen mustard

STRUCTURAL FORMULA



DESCRIPTION

Cyclophosphamide is a sterile white powder containing cyclophosphamide monohydrate. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder and is soluble in water, saline, or ethanol.

DOSAGE FORMS: Tablet, Injection.

MECHANISM OF ACTION

The main effect of cyclophosphamide is due to its metabolite phosphoramide mustard. This metabolite is only formed in cells that have low levels of ALDH. Phosphoramide mustard forms DNA crosslinks between (interstrandcrosslinkages) and within (intrastrandcrosslinkages) DNA strands at guanine N-7 positions. This is irreversible and leads to cell death. Cyclophosphamide has relatively little typical chemotherapy toxicity as ALDHs are present in relatively large concentrations in bone marrow, liver and intestinal epithelium. ALDHs protect these actively

proliferating tissues against toxic effects phosphoramide mustard and acrolein by converting aldophosphamide to carboxyphosphamide that does not give rise to the toxic metabolites (phosphoramide mustard and acrolein)

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Cyclophosphamide is converted by mixed function oxidase enzymes in the liver to active metabolites. The main active metabolite is 4-hydroxycyclophosphamide, which exists in equilibrium with its tautomer, aldophosphamide. Most of the aldophosphamide is oxidised by the enzyme aldehyde dehydrogenase (ALDH) to make carboxyphosphamide. A small proportion of aldophosphamide is converted into phosphoramide mustard and acrolein. Acrolein is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. This can be prevented through the use of aggressive hydration and/or mesna.

PHARMACOKINETICS

Absorption

Cyclophosphamide is rapidly absorbed across the GI membrane following oral administration. Peak effects can be observed after 1—2 hours. The drug gets transformed into active metabolite in the liver and then binds to the acting site.

Distribution

Systemic cyclophosphamide is quickly distributed into the kidneys, intestines, skin, liver and muscle. They have a bioavailability of 75%.

Plasma Protein Binding: > 60%

Metabolism

Extensively metabolized in the liver.

Elimination

The inactive metabolites, as well as a small portion of unchanged drug, are excreted in the urine.

Half-life: 3 to 12 hours.

Paediatric Dose for Nephrotic Syndrome

2-3 mg/kg/day for up to 12 weeks when corticosteroids unsuccessful

OVERDOSAGE

Long-term/overdose use of high cyclophosphamide doses can lead to symptoms such as thinning skin, easy bruising, changes in the shape or location of body fat (especially in your face, neck, back, and waist), increased acne or facial hair, menstrual problems, impotence, or loss of interest in sex.

ROUTE OF ADMINISTRATION: Oral, intramuscular, intravenous.

DOSAGE FORM/ STRENGTH

Powder for injection: 100 mg, 200 mg, 500 mg, 1 g, 2 g
Tablets: 25 mg, 50 mg

INDICATIONS AND CLINICAL USE

Hodgkin's disease; malignant lymphoma; multiple myeloma; leukemia; advanced mycosis fungoides; neuroblastoma; ovarian cancer; breast cancer; and certain other tumors

CONTRAINDICATIONS

- Hypersensitivity to drug
- Severe bone marrow depression
- Breastfeeding

PRECAUTIONS

To be used cautiously in;

- Renal or hepatic impairment, adrenalectomy, mild to moderate bone marrow depression, other chronic debilitating illnesses
- Females of childbearing age
- Pregnant patients.

ADVERSE EFFECTS

CV:cardiotoxicity

GI: nausea, vomiting, diarrhea, abdominal pain or discomfort, stomatitis, oral mucosal ulcers, anorexia, hemorrhagic colitis

GU: urinary bladder fibrosis, hematuria, amenorrhea, decreased sperm count, sterility, acute hemorrhagic cystitis, renal tubular necrosis, hemorrhagic ureteral inflammation

Hematologic:anemia, leukopenia, thrombocytopenia, bone marrow depression, neutropenia

Hepatic: jaundice

Metabolic:hyperuricemia

Respiratory: interstitial pulmonary fibrosis

Skin: nail and pigmentation changes, alopecia

Other: poor wound healing, infections, allergic reactions including anaphylaxis, secondary cancer

DRUG-DRUG INTERACTIONS

Many drugs can interact with cyclophosphamide. Below is a list of drugs which shows interaction with cyclophosphamide.

- Allopurinol, thiazide diuretics: increased risk of leukopenia
- Digoxin: decreased digoxin blood level
- Cardiotoxic drugs (such as cytarabine, daunorubicin, doxorubicin): additive cardiotoxicity
- Chloramphenicol: prolonged cyclophosphamide half-life
- Phenobarbital: increased risk of cyclophosphamide toxicity
- Quinolones: decreased antimicrobial effect
- Succinylcholine: prolonged neuromuscular blockade
- Warfarin: increased anticoagulant effect

CYCLOSPORINE[15-17]

BRAND NAME: IMOSPORIN, SANDIMMUN, NEORAL.

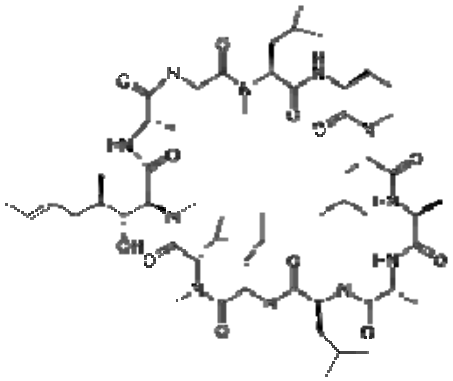
IUPAC NAME:[*R*-[*R**,*R**-(*E*)]]-cyclic(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

CHEMICAL FORMULA:$C_{62}H_{111}N_{11}O_{12}$

MOLECULAR MASS:1202.61 gm/mol

PHARMACOLOGICAL CLASSIFICATION: Calcineurinin Inhibitor

STRUCTURAL FORMULA



DESCRIPTION

Cyclosporine is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauverianivea.*

DOSAGE FORMS: Capsule, Injection.

MECHANISM OF ACTION

Cyclosporine is thought to bind to the cytosolicprotein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of cyclosporine and cyclophilin inhibitscalcineurin, which, under normal circumstances, is responsible for activating the transcription of interleukin 2. In T-cells, activation of the T-cell receptor normally increases intracellular calcium, which acts via calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor NF-AT (nuclear factor of activated T-cells), which moves to the nucleus of the T-cell and increases the activity of genes coding for IL-2 and related cytokines. Cyclosporine prevents the dephosphorlyation of NF-AT by binding to cyclophilin. It also inhibits lymphokine production and interleukin release and, therefore, leads to a reduced function of effector T-cells. It does not affect cytostatic activity. Cyclosporine affects mitochondria by preventing mitochondrial permeability. This is not the primary mechanism of action for clinical use, but is an important effect for research on apoptosis.

Cyclosporine is believed to elicit its effects by directly binding to the cyclophilin D protein (CypD) that constitutes part of the mitochondrial permeability transition pore (MPTP) and by inhibiting the calcineurin phosphatase pathway. The MPTP is found in the mitochondrial membrane of cardiac myocytes (heart muscle cells) and functions to move calcium ions (Ca^{2+}) into the mitochondria. When open, Ca^{2+} enters the mitochondria, disrupting transmembrane potential (the electric charge across a membrane). If unregulated, this can contribute to mitochondrial swelling and dysfunction. To allow for normal contraction, intracellular Ca^{2+} increases, and the MPTP in turn opens, shuttling Ca^{2+} into the mitochondria. Calcineurin is a Ca^{2+}-activated phosphatase (enzyme that removes a phosphate group from substrate) that regulates cardiac hypertrophy. Regulation occurs through NFAT (nuclear factor of activated T-cells) activation, which, when dephosphorylated, binds to GATA and forms a transcription factor (protein that can bind DNA and alter the expression of DNA) with ability to control the hypertrophic gene (2). Activation of calcineurin causes increases in hypertrophy.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Cyclosporine is the most effective drug for the prevention and treatment of graft rejection reaction. It is routinely used in the renal, hepatic, cardiac, bone marrow and other transplantations. It has low bioavailability and it depends on the presence of bile for its action.

PHARMACOKINETICS

Absorption

Cyclosporine is absorbed across the GI membrane following oral administration. Peak effects can be observed after 12 hours. The drug gets transformed into active metabolite in the liver and then binds to the acting site.

Distribution

Systemic cyclosporine is quickly distributed into the kidneys, intestines, skin, liver and muscle.

Plasma Protein Binding: 90%

Metabolism

Extensively metabolized in the liver.

Elimination

The inactive metabolites, as well as a small portion of unchanged drug, are excreted in sthe bile.

Half-life: 8 to 27 hours.

Paediatric Dose

- 4-12 hr pre-transplant: 15 mg/kg PO for 1 dose
- 1-2 wk post-transplant: 15 mg/kg PO qDay
- Reduce 5% per week until: 5-10 mg/kg PO qDay
- 4-12 hours pre-transplant IV: 5-6 mg/kg IV for 1 dose over 2-6 hr

OVERDOSAGE

Long-term/overdose use of high cyclosporine doses can lead to high poisoning of the drug. Overdose can cause nausea, vomiting, pain in your upper stomach, loss of appetite, jaundice (yellowing of the skin or eyes), and urinating less than usual or not at all.

ROUTE OF ADMINISTRATION: Oral, intramuscular, intravenous.

DOSAGE FORM/ STRENGTH

Injection:1, 5, 50 ml.
Capsules: 25 mg, 50 mg, 100 mg.

INDICATIONS AND CLINICAL USE

This medication is used to prevent organ rejection in people who have received a liver, kidney, or heart transplant. It is usually used along with other medications to allow your new organ to function normally.This drug may also be used to prevent rejection in other types of organ transplants (e.g., cornea, pancreas) or bone marrow transplant. It may also be used to treat other conditions that may be helped by affecting the immune system (e.g., Crohn's disease, ulcerative colitis).

CONTRAINDICATIONS

- Hypersensitivity to drug
- Severe bone marrow depression
- Breastfeeding

PRECAUTIONS

To be used cautiously in;

- Renal or hepatic impairment, adrenalectomy, mild to moderate bone marrow depression, other chronic debilitating illnesses
- Females of childbearing age
- Pregnant patients.

ADVERSE EFFECTS

>10%

Tremor (12-55%)
Nephrotoxicity (32%)
Hypertension (26%)
Infection (3-25%)
Headache (2-25%)
Nausea (23%)
Hirsutism (21%)
Hypertrichosis (5-19%)
Female reproductive disorder (5-19%)
Gum hyperplasia (2-16%)
Triglycerides increased (15%)
Abdominal discomfort (1-15%)
URI (1-14%)
Diarrhea (3-13%)
Dyspepsia (2-12%)
Leg cramps (2-12%)
Parathesia (1-11%)

1-10%

Acne

Convulsions

Pruitus

Hyperkalemia, hypomagnesemia

Pancreatitis

Hepatotoxicity

Flu-like syndrome

DRUG-DRUG INTERACTIONS

Many drugs can interact with cyclosporine. Below is a list of drugs which shows interaction with cyclosporine.

- Amphotericin b deoxycholate

  Amphotericin b deoxycholate and cyclosporine both increase nephrotoxicity and/or ototoxicity.
- Bosentan

  Cyclosporine increases levels of bosentan by decreasing metabolism.
- Cidofovir

  Cidofovir and cyclosporine both increase nephrotoxicity and/or ototoxicity.
- Neomycin

  Cyclosporine and neomycin po both increase nephrotoxicity and/or ototoxicity.
- Pitavastatin

  Cyclosporine increases levels of pitavastatin by decreasing metabolism.
- Simvastatin

  Cyclosporine will increase the level or effect of simvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Increased risk for rhabdomyolysis with drugs that increase simvastatin systemic exposure.

REVIEW OF LITERATURE[18-48]

- **AravindBaggaetal.**studied about the nephrotic syndrome in children. Long term effects such as thromboembolic episodes, hyperlipidemia and [prolonged steroid therapy were recognized. Remission of proteinuria and frequency of relapse pattern was also studied. The disease was treated with levamisole, cyclophosphamide, cyclosporine and mycophenolatemofetil in steroid resistant patients. The treatment was beneficial in most of the cases and remission was achieved sooner. Reduction of proteinuria was also possible in children, using angiotensin converting enzyme inhibitors.

- **McKinney PA et al.** designed a study to identify recent time trends and ethinic patterns oh childhood nephrotic syndrome. A population-based cohort of children (0-15 years) diagnosed according to strict criteria with nephrotic syndrome (NS) was ascertained within the northern UK region of Yorkshire between 1987 and 1998. South Asian ethnicity was assigned based on the child's full name using a dedicated computer algorithm and expert individual checks. NS was diagnosed in 194 children, 170 (88%) of whom were steroid sensitive. Over the 12-year study period incidence rates of steroid sensitive NS were fairly stable although south Asian children displayed significantly higher rates than non-south Asians ($P<0.01$). The size of our population-based series reflects the relative rarity of paediatric nephrotic syndrome but is nonetheless recent and includes larger numbers than previous reports. The absence of any increase in incidence over the last decade contrasts with other paediatric immune mediated conditions such as asthma and diabetes.

- **Srinivastava et al.** designed a clinicopathological study of 206 Indian children with nephrotic syndrome showing a primary renal cause in 195 (96%), of which 77% were boys. In 126 children (96 boys, 30 girls) onset of the disorder occurred before the age of 5 years. Renal biopsy showed minimal lesions in 150 patients in 85 of these biopsy was done 3 months to 16 years after onset of the nephrotic syndrome. Significant renal histological abnormalities in 45 cases were labelled as mesangiocapillary 8,

mesangioproliferative 4, proliferative with extensive crescents 2, membranous 3, focal segmental glomerulosclerosis 9, focal global glomerulosclerosis 2, advanced nonspecific 8, and mild proliferative 9. Clearance of proteinuria with corticosteroid therapy was practically confined to patients with minimal or mild renal histological changes and the findings suggest that the pattern of idiopathic nephrotic syndrome in Indian children is similar to that reported from Western countries.

- ✓ **White et al.** carried out Renal-biopsy specimens from 145 children with the nephrotic syndrome and were placed in four morphological categories: minimal changes (111 patients), focal glomerulosclerosis (12), proliferative glomerulonephritis (20), and epimembranous nephropathy (2). These were then correlated with the clinical and laboratory findings, and the response to corticosteroid and cytotoxic therapy. Children with minimal changes, generally had highly selective proteinuria were 97% were steroid-responsive, though most later relapsed. Children with structural glomerular alterations, who were mainly girls and of school age, usually had moderately or poorly selective proteinuria, while haematuria and hypertension were additional features. Only 9% responded to steroids. Of the three varieties of proliferative glomerulonephritis encountered in this series, the membranoproliferative form was characterised by low serum C3 (β1c-globulin) levels and a chronic course, while the mesangial type was associated with normal C3 levels and a favourable outcome despite resistance to conventional therapy. It seems that the likelihood of an individual responding to cytotoxic drugs can be predicted from his initial steroid response alone.

- ✓ **Indian pediatric nephrology group** designed a study to revise and formulate recommendations for management of steroid sensitive nephroticsyndrome.The need for adequate corticosteroid therapy at the initial episode was emphasized. It is proposed that patients with frequently relapsing nephrotic syndrome should, at the first instance, be treated with long-term, alternate-day prednisolone. The indications for use of alternative immunosuppressive agents, including levamisole, cyclophosphamide, mycophenolatemofetil and cyclosporin are outlined. The principles of dietary therapy, management of

edema, and prevention and management of complications related to nephrotic syndrome are described. These guidelines, formulated on basis of current best practice, are aimed to familiarize physicians regarding management of children with steroid sensitive nephrotic syndrome.

- ✓ **Constantinescu et al.** carried out a study to identify factors at initial presentation that could predict the relapse pattern in the first year after diagnosis, without taking into consideration the histopathology found on renal biopsy. Of 70 patients, 14 were excluded because of insufficient data. There were 38 males and 18 females, giving a male:female ratio of 1.8:1. Median age at presentation was 3.25 years (range: 1.5–13). Of all the patients, 23 were IR (41.1%), 9 were FR (16.1%), and 24 were SD (42.9%). Median days to remission were 10 (range: 2–60), on Prednisone 60 mg/M^2 daily. Hematuria was present initially in 26 patients (46.4%), and absent in 30 (53.6%).However, using a stratified analysis based on the presence or absence of hematuria, they found that if the remission occurred within the first week of therapy, the patients without hematuria were more likely to be IR. They concluded that of all the presenting features, the rapidity of initial response to steroid therapy combined with the presence of hematuria, could predict future relapses and should be well documented.

- ✓ **Niaudet et al.** made a review to show the results of both uncontrolled and controlled studies of the therapeutic effects of cyclosporine in steroid-sensitive/dependent idiopathic nephrosis and in steroid-resistant idiopathic nephrosis . Cyclosporine was efficient in up to 80% of patients with steroid-sensitive/dependent idiopathic nephrosis. Although cyclosporine is less efficient in patients with steroid-resistant idiopathic nephrosis, a few studies seem to indicate that this drug may be successful in some patients, especially if combined with corticosteroids. The main worrisome side effect of cyclosporine is chronic nephrotoxicity, which should be differentiated from acute or "functional" toxicity. Follow-up studies including pre treatment and post treatment renal biopsies show a lack of correlation between structural damage and renal function, suggesting that a histologic examination of the

renal parenchyma is the only reliable way of evaluating chronic cyclosporine nephrotoxicity.

- ✓ **Singh et al.** designed a study which describes the use and efficacy of cyclosporine (CSA) for the treatment of refractory NS in 83 children seen over a 10-year period. The histological diagnosis leading to the NS was focal segmental glomerulosclerosis (FSGS) in 51% (n = 42), IgM nephropathy in 20% (n = 17), membranoproliferative glomerulonephritis in 10% (n = 8), lupus nephritis in 6% (n = 5), human immunodeficiency virus (HIV) nephropathy in 5% (n = 4), minimal change disease in 7% (n = 6), and membranous nephropathy in 1% (n = 1) of patients. During CSA therapy the mean proteinuria, urine albumin and Serum cholesterol decresed to a greater extent. There was a rise in serum creatinine following the use of CSA in patients with FSGS, lupus nephritis, and HIV nephropathy; however the elevated serum creatinine was only significant in patients with FSGS. At the end of the study period, 20 patients had reached ESRD, of which 11 had FSGS, 5 had lupus nephritis, and 4 were patients with HIV nephropathy. Fifty-four patients were in remission at the end of the study period (48 with proteinuria < 100 mg/24 h and 6 with proteinuria < 500 mg/24 h). In conclusion, among children with refractory NS, CSA induced a remission in a large proportion. However toxicity, as noted by the rise in serum creatinine, was observed in several patients.

- ✓ **Ponticelli.Cet al** carried out a study compare the efficacy (maintenance of remission), safety and tolerability of cyclosporin (CsA) with those of cyclophosphamide in patients with steroid-dependent or frequently relapsing nephrotic syndrome (NS). Seventy-three patients with steroid-sensitive idiopathic NS admitted to the study were randomly assigned to cyclophosphamide (2.5 mg/kg/day) for 8 weeks or CsA (5 mg/kg/day in adults, 6 mg/kg/day in children) for 9 months, tapered off by 25% every month until complete discontinuation at month 12. Relapse-free survival; number of N.S. relapses/patient/year; cumulative dose of prednisone/patient; laboratory investigations (kidney and liver functions, haematological parameters); incidence of adverse events were measured. The study concluded

that tolerance to the two drugs was generally good. The CsA-related side-effects were mild and disappeared after drug discontinuation.

- ✓ **Rennert WP et al.** conducted a therapeutic trial to compare the efficacy of cyclophosphamide with that of prednisone in two categories of children with the nephrotic syndrome: patients who continue to have proteinuria after 8 weeks of prednisone therapy (early non-responders) and patients who respond initially but who subsequently have multiple exacerbations of their disease (frequent relapsers). The results in early non-responders indicate that the proportion of patients who lost their proteinuria was similar in both treatment groups. However, proteinuria subsided earlier in those who received cyclophosphamide. The results in frequent relapsers confirm previous reports that cyclophosphamide is more effective than prednisone in inducing a lasting remission. The study also revealed that frequent relapsers are much less likely to relapse while receiving cyclophosphamide than they are during intermittent therapy with prednisone.

- ✓ **Fakhrossadat M and Yaser S et al.**designed a study to evaluate thesteroid response pattern and outcome of idiopathic NS (INS) in a pediatric referral hospital innorthwestIran.Medical records of all admitted children under 14 years of age with INS inthe Children's Hospital of Tabriz, from 1999 to 2010 were studied retrospectively. A total of 165 patients with INS, with a mean age of 4.98 ± 2.61 years were studied. Male to female ratio was 2:1. Duration of follow-up was 5.36 ± 2.2 years (1–10 years). A total of 124 patients (75.2%) responded to steroids, and 41 patients (24.8%) were steroid resistant. Frequency of hematuria ($P = 0.01$) and steroid resistance ($P = 0.005$) in girls was significantly higher than boys. Patients with steroid resistance had a higher frequency of hematuria ($P = 0.001$) and a higher mean age ($P = 0.017$) in comparison with steroid responders. The remission and relapse pattern was also studied. The study concluded that demographics, histological features, and outcome of INS were similar to western countries

- ✓ **Safaei A.A.S.L and Maleknejad S et al.**studied the clinical and biochemical parameters at the time of diagnosis of nephrotic syndrome and the histopathological distribution of different subtypes of INS and drug response pattern. There were 29 (66%) males and 15 females (34%). The mean age of NS was 4.87±3.24 years. Facial edema was found in 42 (95%), microscopic hematuria in 10 (23%), gross hematuria in 2 (4.5%), and hypertension in 5 (11.2%) of patients. In 17 children who underwent biopsy, focal segmental glomerulosclerosis was the most common pathologic finding (41%).

  Other subtypes included minimal change in three (18%), membranoproliferative glomerulonephritis in 1(5.8%), diffuse proliferative glomerulonephritis in 2 (11.6%), membranous glomerulonephritis in 1 (5.8%), and diffuse mesangial proliferation in 3 (17.5%) of cases. At the time of hospital admission, peritonitis were present in five (11.4%), pneumonia and upper respiratory infection (sinusitis) in eight (18%), cellulitis in two (4.5%). Among 44 children with NS, 29 (66%) were steroid sensitive cases, nine (20.5%) were steroid resistant and six (13.5%) were steroid dependent. Among patients with steroid sensitive NS, 37% were without relapsers, 38.8% frequent relapsers and 26.4% were infrequent relapsers. These results suggested that there were differences between seasons of incidence and response to treatment with corticosteroid.

- ✓ **Mubharaketal.**undertook this study to determine the pattern of glomerulopathies based on renal biopsies studied by light (LM), immunofluorescence (IF), and electron microscopy (EM).). All children (≤18 years) with INS in whom renal biopsy was performed were included. Renal biopsies were studied by LM, IF, and EM. Of 538 children, 347 (64.4%) were male and 191 (35.5%) were female. Mean age was 9.79 ± 4.59 years. The histopathological lesions comprised: minimal change disease (MCD) and its variants, 43.8%; focal segmental glomerulosclerosis (FSGS), 38.14%; membranous glomerulonephritis (GN) (MGN), 7.96%; mesangioproliferative GN (MesPGN), 4.81%; mesangiocapillary GN (MPGN), 3.14%; IgA nephropathy (IgAN), 1.11%; and other rare lesions. MCD and its variants are the leading cause of overall INS in children, followed by FSGS, which is the

predominant pathology in steroid-resistant and adolescent nephrotic syndrome (NS). The study defines the true pattern of glomerulopathies in childhood INS for the first time in Pakistan.

- ✓ **Madani A and Fahimi D etal.**carried out the study determine the rate of steroid responsiveness in children with INS that referred to Children's Medical Center since 1995 to 2007. A total of 238 patients were enrolled in the study. Kidney biopsy was performed in 79 cases. Minimal change lesion (MCL) was the most common (36.7%) pathological diagnosis. Steroid responsiveness was found in 81.5% of all cases including: 96% of MCL (consisting of biopsy proven cases and presumed ones), 32% of focal and segmental glomerulosclerosis, 73% of diffuse mesangial proliferation and 58% of membranoproliferative glomerulonephritis patients. During minimal follow up period of 12 months, there were 194 patients in remission, 32 patients with active NS, and 12 patients in ESRD. Study results showed that 81.5% of all patients, 96.2% of MCL and 32% of FSGS patients initially responded to steroid therapy.

- ✓ **Fuchshuber A and Gribouval et al.** studied the Clinical and Genetic Evaluation of Familial Steroid-Responsive Nephrotic Syndrome in Childhood. The clinical course in terms of age at onset, symptoms during the initial phase, renal morphology, and outcome was evaluated. Furthermore, linkage to *NPHS2*, the gene for autosomal-recessive steroid-resistant INS on chromosome1, was examined. By linkage studies and mutational analysis, familial SSINS was found to be genetically distinct from *NPHS2*. This was the first report of a large cohort of familial SSINS.

- ✓ **Pontivelli C, Rizzon G et al.** carried out a randomized trial of cyclosporine in steroid-resistantidiopathicnephrotic syndrome. They compared the efficacy (induction of remission) and safety cyclosporine (CsA) with those of supportive therapy in patients with steroid-resistant idiopathic nephrotic syndrome (INS). The study shows that CsA can bring about remission in some 60% of patients with steroid-resistant INS. In patients with normal renal

function and without severe hypertension,CsA at the therapeutic scheme adopted did not produce severerenal or extrarenal toxicity.

- ✓ **Anochie I, Eke F and Okpere A** designed a study to find out the childhood nephroticsyndrome : change in pattern and response to steroids. The study included 14 girls and 14 boys with NS. The peak age was 1-4 years. Twenty (71.4%) children had idiopathic nephrotic syndrome (INS). Four had chronic renal failure, one had sickle cell disease (HbSS), two were positive to human immunodeficiency virus (HIV) 1 and 2, and one had pulmonary tuberculosis. Anemia was found in 13 patients, while 17 had Plasmodium falciparum. Plasmodium malariae and hepatitis-B surface antigen were not isolated. Renal biopsy was performed in four patients and revealed minimal-change disease in one child, focal segmental glomerulosclerosis in two and no conclusive result in one patient. Oral prednisolone was used in INS. After one month of therapy, 16 of 20 responded, of which 12 (75%) were <5 years. The NS relapsed in 15 of 16 steroid-sensitive patients. Cyclophosphamide and levamisole were used in four and one patients with FRNS, respectively. Four (14.3%) patients died; all were secondary NS. The study concluded that INS remains common in our center, and the majority respond to steroid therapy.

- ✓ **Schulman L and Kaise A et al.** studied the utility of steroid response in classifying childhood nephrotic syndrome. They reviewed 119 biopsies in 92 children aged 1 to 16 years who had been followed for a mean of 7.2 years. Biopsy specimens were classified as showing focal glomerulosclerosis (FSGS) in 39 children, as showing lipoid nephrosis in 28, and as questionable in another 25 with either focal global sclerosis, IgM nephropathy, or mesangial prominence and tubular changes. The length of the remission after therapy with chlorambucil or cyclophosphamide was determined in 84 children. The remission and relapse pattern was aso being studied and concluded by the them along with the histopathological changes.

- ✓ **Hasan O and Salman O et al.** carried out a study on management and outcome of steroid resistant nephrotic syndrome in children. Study wqs carried out in in 73 childdren with SRNS. The mean follow-up duration was 6.0 ± 4.2 years. The type of resistance (early orlate) was associated with the responsiveness to immunosuppressives.Response to any of the immunosuppressive drugs determined theresponsiveness to other immunosuppressive drugs. Cyclosporinewas more effective than cyclophosphamide as initial therapy. Themean kidney survival time was 11.62 years. Kidney survival rateswere 94.6%, 70.0%, 56.0%, and 34.0% at 1, 5, 10, and 15 years,respectively, in patients with initial resistance to steroid, while thesewere 100%, 100%, 83.0%, and 83.0% in those with late resistance,respectively. They showed that patients with late steroid resistance hadbetter response to immunosuprressive drugs than patients with earlyresistance.

- ✓ **Filler G** designed a study to determine the sequential therapy of childhoodnephrotic syndrome (NS) with presumed minimalchange nephropathy using the evidence from clinicaltrials. Meta-analysis of 22 randomized controlled trials was performed, using frequency of relapse and side effects of therapeutic regimes. They concluded that Children with initial onset of NS should be treated with prednisone at a dose of 60 mg/m2/day for 6 weeks, followed by a dose of 40 mg/m2/48 h for at least another 6 weeks. If steroid toxicity for treatment of relapsing NS requires alternative treatment, cyclophosphamide (2 mg/kg/day for at least 8 weeks) remains the drug of choice with a curative potential. If children still relapse after alkylating agents, levamisole may serve as an alternative only for frequent relapsing NS, whereas steroid-dependent NS should be treated with cyclosporine.

- ✓ **Gaudio KM and Krassner et al.** carried a long-term clinical course of 60 children with steroid-responsive nephrotic syndrome, observed for a minimum of 10 years from onset, was studied (mean 14.5 +/- 0.5 years). All 20 children treated with cyclophosphamide because of steroid-induced side effects developed complete remissions of the nephrotic syndrome. In contrast, only 48% of patients treated with prednisone alone were in remission at last follow-

up (P = .06). Ten of the children treated with cyclophosphamide had the minimal change lesion prior to therapy; 90% of these had permanent remissions. Only 50% of the six children with focal glomerulosclerosis and four children with mesangial proliferation have had permanent remissions. None of the patients developed renal insufficiency. Study showed that children with severe growth impairment demonstrated dramatic catch-up growth when treated with cyclophosphamide with SD scores increasing from -2.29 +/- 0.8 to -0.43 +/- 0.6 (P less than .05).

- ✓ **Durkan AM and Hodson ME et al.** studied about the Immunosuppressive agents in childhood nephrotic syndrome. Seventeen trials involving 631 children were identified. Cyclophosphamide [3 trials; relative risk (RR) 0.44, 95% confidence interval (CI), 0.26 to 0.73] and chlorambucil (2 trials; RR 0.13, 95% CI, 0.03 to 0.57) significantly reduced the relapse risk at 6 to 12 months compared with prednisone alone. Study concluded that Cyclophosphamide, chorambucil, cyclosporine, and levamisole reduce the risk of relapse in children with relapsing SSNS compared with prednisone alone. Clinically importantdifferences in efficacy among these agents are possible, and further comparative trials are still needed.

- ✓ **Gulati S, Kher V, Sharma RK, Gupta A.** conducted a study comprising 127 children with nephrotic syndrome. They were treated with oral prednisolone according to the APN protocol. Based on the subsequent response these children were classified into different steroid response categories on follow-up. Of the 116 children with follow-up of more than six months, infrequent relapsers constituted the majority (37.9%). The frequency of other steroid response categories was as follows: frequent relapsers (21.6%), steroid-dependent (18.1%), initial non-responders (17.3%) and subsequent non-responders (5.1%). The factors predicting a poor response to standard prednisolone therapy in our study were age of onset more than eight years, male sex, hypertension, microscopic haematuria and presence of non-minimal change nephrotic syndrome lesions on histopathology.

- ✓ **Takeda A, Ohgushi H, Niimura F, Matsutani H** studied the Long-term effects of immunosuppressants in steroid-dependent nephrotic syndrome. In order to elucidate long-term effects of immunosuppressants, they studied 60 children with steroid-dependent nephrotic syndrome who were treated with three immunosuppressants: cyclophosphamide (n=34), chlorambucil (n=11), and cyclosporin A (n=15). Each relapse before and after the administration of immunosuppressants was evaluated longitudinally in terms of the relapse-free period and the maintenance dose of prednisolone required. the relapse-free period after subsequent relapses as compared with the previous relapse was longer in the cyclophosphamide group, similar in the chlorambucil group, and shorter in the cyclosporin A group. These findings suggest that the effects of cyclophosphamide are long lasting, while those of chlorambucil and cyclosporin A are of short duration.

- ✓ **Frange P, Frey MA, DeschênesG.**carried out a study on Immunity and immunosuppression in childhood idiopathic nephrotic syndrome. They said that steroids were used to treat NS over 50 years but due to efficiency of levamisole and cyclophosphamide are much more limited than previously reported and cyclosporin nephrotoxicity might severely impair renal function following long-lasting treatment as well as it may paradoxically increase the activity of the disease. An alternate strategy to those currently adopted would use cyclosporin as the first-line steroids-sparing treatment during a very limited period, awaiting favourable ageing of patients and natural dampening activity of the disease to a full efficiency of alkylating agents. Compared to cyclophosphamide and cyclosporin, the relative safety of levamisole is encouraging to a more frequent uses. Its association to a full dose of prednisone in the treatment of the inaugural episode should be investigated. According to the limitations of those therapies, emerging drugs as mycophenolate might be worthwhile in the treatment of nephrotic patients.

- ✓ **Durkan A, Hodson E, Willis N, Craig J.**designed a study to evaluate the benefits and harms of non-corticosteroid immunosuppressive agents in relapsing SSNS in children. Two reviewers independently reviewed all eligible studies for inclusion, assessed study quality and extracted data. The

principle outcome measure was the number of children with and without relapse after six and 12 to 24 months. Secondary outcomes sought were the mean time to next relapse, the mean number of relapses per year and adverse events. They concluded that Eight weeks courses of cyclophosphamide or chorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone. Clinically important differences in efficacy among these agents are possible and further comparative trials are still needed. Meanwhile choice between these agents depends on physician and patient preferences related to therapy duration and the type and frequency of complications.

- ✓ **Chen SY, Wu CY, Tsai IJ, Tsau YK.**studied the treatment course of steroid-dependent nephrotic syndrome: emphasized on treatment effect. Forty-six children with SDNS were enrolled in this retrospective uncontrolled study. In addition to prednisolone, patients were treated with cyclophosphamide as a first-line alternative drug. Children who still had SDNS despite cyclophosphamide therapy received chlorambucil, levamisole or another course of cyclophosphamide. The treatment responses were recorded and the mean duration of follow up was 96 months. Seventeen patients (37%) experienced no relapse after cyclophosphamide therapy. Twenty-five patients (54%) had varied responses. Only four patients showed no effect. Children who still had SDNS despite cyclophosphamide therapy received second or more alternative drugs. Cyclophosphamide with or without chlorambucil resolved steroid-dependency in 33 of 46 (72%) children who either had complete remission or developed steroid-sensitive, rather than steroid-dependent, nephrotic syndrome.

- ✓ **Takeda A, Takimoto H, Mizusawa Y, SimodaM.**carried out the study for the Prediction of subsequent relapse in children with steroid-sensitive nephrotic syndrome. They examined the clinical course of 467 relapses in 121 steroid-sensitive nephrotic children to elucidate the risk factors for subsequent relapse, using the Cox proportional-hazards regression model. Gender, age at onset, duration of illness from onset, prednisolone dosage at the most-recent relapse, and regimens of initial steroid therapy at onset were not associated

with risk. Relapse within the 1st year was a powerful independent predictor of subsequent relapse irrespective of the duration of illness. Patients treated with cyclophosphamide for 12 weeks had a significantly longer remission than those treated with prednisolone alone. Their results suggested that early relapse after onset and/or a short remission period just before recent relapse are independent risk factors for subsequent relapse. Cytotoxic therapy has serious adverse effects and its effect may be limited. Their results may be helpful in deciding on the suitability of cytotoxic drugs.

- ✓ **Sudesh Paul Makker.**designed a study for the prospective comparison of prednisone plus ciclosporin and prednisone alone in pediatricnephrotic syndrome. A randamoized trial was being done in children with NS. Two group of people were used, one group was treated with prednisolne plus ciclosporin and the other with prednisolone alone. The results concluded that the relapse pattern was reduced in children who were treated with prednisolone plus ciclosporin when compared to children treated with prednisolone alone.

- ✓ **Hoyer PF, BrodehJ.**made a study on Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. Patients with an initial attack of nephrotic syndrome were randomly allocated to treatment with 6 wk of 60 mg/m(2) per d prednisone followed by 6 wk of 40 mg/m(2) per 48 h (Pred group) or to the same prednisone treatment plus 8 wk of cyclosporine (Pred+CsA group). The primary end point was first relapse; follow-up was truncated at 2 yr. The significant benefit for adding CsA was lost after 9 to 12 mo. GFR remained unchanged. The subsequent treatment rate with cyclophosphamide was lower in the CsA group (five versus 12 patients) after 2 yr. With the use of logistic regression statistics, children who were younger than 7 yr showed a significantly better sustained remission rate with initial CsA treatment for the 2-yr.

- ✓ **Richard S. Trompeter**.studied the effect of Immunosuppressive therapy in the nephrotic syndrome in children. The high incidence of remission and prevention of relapse of minimal change nephrotic syndrome (MCNS) in children, produced by corticosteroids is reviewed. Children with frequently relapsing, steroid-dependent MCNS will usually enter remission following treatment with an alkylating agent such as cyclophosphamide. In about 50% no further relapse was experienced. The results of recent experience using cyclosporinA immunosuppression suggested a beneficial effect associated with steroid responsiveness. Approximately 30% of children with focal segmental glomerulosclerosis enter remission following treatment with corticosteroids. Some 30% require dialysis and transplantation within 5 years of diagnosis and immunosuppressive therapy to prevent deterioration of renal function is probably justified.

AIM AND OBJECTIVE

AIM

The aim of the study was to determine the steroid responsive pattern and as well as the role of cyclophosphamide and cyclosporine in childhood nephrotic syndrome.

OBJECTIVES

The present study was designed to carry out the following objectives listed below:

- ✓ To analyse the incidence and prevalence of primary nephrotic syndrome in children up to 14 years of age.
- ✓ To study the clinical and biochemical parameters and the histopathological distribution of different subtypes of nephrotic syndrome and drug response pattern
- ✓ To assess the responsiveness of corticosteroid therapy given over a period of 24 week according to ISKDC regimen.
- ✓ To assess relapse pattern and remission pattern of nephrotic syndrome in children.
- ✓ To analyse the incidence of steroid resistant nephrotic syndrome in children.
- ✓ To assess usefulness of cyclophosphamide and cyclosporine in steroid resistant nephrotic syndrome.

PLAN OF THE WORK

The present dissertation was undertaken to study the incidence of childhood nephrotic syndrome and steroid responsive pattern.

- ✓ Collection of patients admitted with nephrotic syndrome upto 14 years of age in nephrology unit of the hospital.
- ✓ To find out the etiology of nephrotic syndrome from case history.
- ✓ To study the elevation in clinical parameters.
- ✓ To study the histopathological distribution of different sub types of nephrotic syndrome and drug response pattern.
- ✓ To observe the effect of cyclophosphamide and cyclosporine in steroid resistant nephrotic syndrome.
- ✓ To study the relapse and remission pattern of nephrotic syndrome.
- ✓ To analyse the data in consultation with respective Nephrologist.
- ✓ Presentation of results.

BACKGROUND OF THE STUDY

This prospective study was conducted at Nephrology department in **"MEENAKSHI MISSION HOSPITAL AND RESEARCH CENTER" (MMHRC),** Madurai.

MEENAKSHI MISSION HOSPITAL AND RESEARCH CENTER

This hospital is located in lake area at Madurai. This is a 750 plus bedded hospital built in late 20^{th} century by Dr.SETHURAMAN (FOUNDER). The hospital was especially built for lower realms of humanity in our country. The multidisciplinary hospital provides medical and surgical services at higher levels. It is also a deemed autonomous teaching hospital which have academic programs for paramedical disciplines.

This study was conducted between July – December 2011. The children admitted with nephrotic syndrome in nephrology department were enrolled and the cause for the disease, corresponding variations in laboratory values, histopathological changes and its clinical management were also studied.

METHODOLOGY

STUDY DESIGN

A Singlecenter, Randomized and Prospective study

OFFICIAL TITLE

Childhood Nephrotic Syndrome and Steroid responsiveness – A Single Center Study In South India.

STUDY POPULATION

The study group included 120 children with age up to 14 years.

SETTING

The study was conducted in children with nephrotic syndrome at Meenakshi Mission Hospital and Research Center, Madurai, which is providing specialized healthcare for peoples from Madurai.

INCLUSION CRITERIA

- ✓ Children up to 14 years of age.
- ✓ Children with nephrotic syndrome
- ✓ Children with elevated clinical parameters
- ✓ Children who are resistant to steroids

EXCLUSION CRITERIA

- ✓ Children with ESRD
- ✓ Children with other complications along with nephrotic syndrome

DATA COLLECTION

The data has been collected from the Nephrology unit. A Performa was designed to collect the clinical and biochemical parameters as well as the drug response pattern.

METHODS

Medical records of children up to age of 14 years with nephrotic syndrome were studied. All patients fulfilled the international study of kidney disease in children (ISKDC) criteria for the diagnosis of NS: nephrotic-range proteinuria (urinary spot protein/creatinine> 2.0), hypoalbuminemia (serum albumin < 2.5 g/dl), hyperlipidemia (serum cholesterol > 200 mg/dl), and edema. The study parameters included age, sex, presenting symptoms, complete blood count, urinalysis and microscopy, 24-hour urinary protein excretion, creatinine clearance, serum electrolytes, serum urea and creatinine levels, treatment provided and outcome.

Kidney biopsy was carried out in the following situations a) Frequent relapses and b) Steroid non responders. Based on the biopsy reports the various types of nephrotic syndrome were found out.

The response to treatment was classified according to the definitions from ISKDC:

(a) steroid sensitive - complete resolution of proteinuria within eight weeks of prednisolone therapy.

(b) Steroid resistance - failure to respond to eight consecutive weeks of treatment with prednisolone at 2 mg/kg/day.

(c) Frequent relapses - two or more episodes of nephrosis within six months of the initial response or four or more within a 12-month period (not related to changes in prednisolone dose).

(d) Remission: Urinary protein excretion <4 mg/m^2/h; nil or trace by dipstick on spot sample for 3 consecutive days.

Patients who had no indication for renal biopsy were treated with prednisolone 60 mg/m^2/day for 4–6 weeks followed by prednisolone 40 mg/m^2 on alternate days for a further 4 weeks. The prednisolone dose was then tapered and discontinued over the next 2–3 months. Steroid resistant's and frequent relapsers underwent treatment with other alternative agents including cyclophosphamide (2–3 mg/kg/day for 8–12 months) and cyclosporine (3–6 mg/kg/day). Using a standardized data-sheet, we obtained data regarding age, sex, presenting features, laboratory findings, response pattern,treatment and biopsy results.

PARAMETERS MEASURED

The various parameters studied are

- ✓ Haemoglobin
- ✓ ESR
- ✓ B.Glucose
- ✓ P. urea
- ✓ P.Creatinine
- ✓ P. Cholesterol
- ✓ Plasma Total Protein
- ✓ P. Albumin
- ✓ Protein / Creatinine ratio
- ✓ Pus, Epithelial cells
- ✓ RBC

At first, the baseline values of all the above parameters were measured for all study subjects and it was compared with the values obtained at the end-course of the study period after treatment with the study drugs.

STATISTICAL ANALYSIS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of Graph Pad instat (GPI V3.0).

Using these software mean, Standard Deviation (SD), Standard Error Mean (SEM) and p values was calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONS AND RESULTS

For this study, medical records of 120 paediatric patients with nephrotic syndrome were collected and analyzed. These patients were selected according to the inclusion and exclusion criteria. Following observations were made under our study.

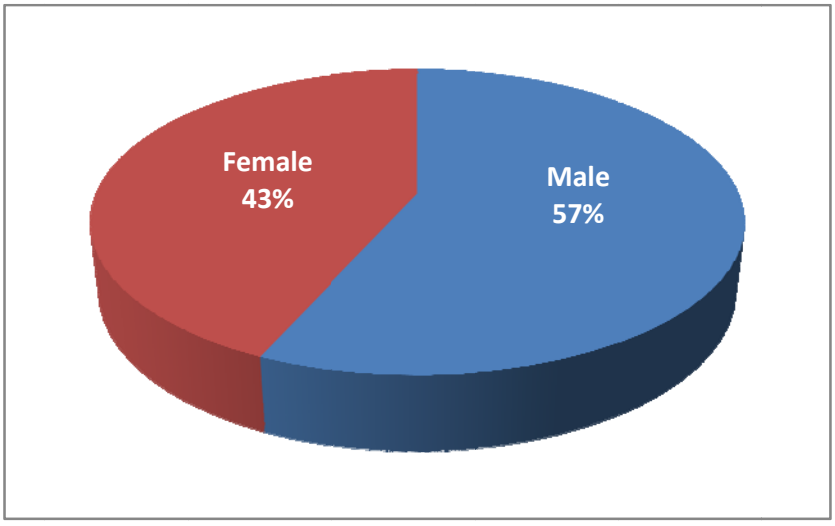
SEX DISTRIBUTION:

Among the study subjects of 120 patients, 68 patients were Male (57%) and 52 patients were Female (43%).

TABLE NO: 1 GENDER DISTRIBUTION

S.no	Sex	Number of patients
1	Male	68
2	Female	52

FIGURE NO: 2GENDER DISTRIBUTION



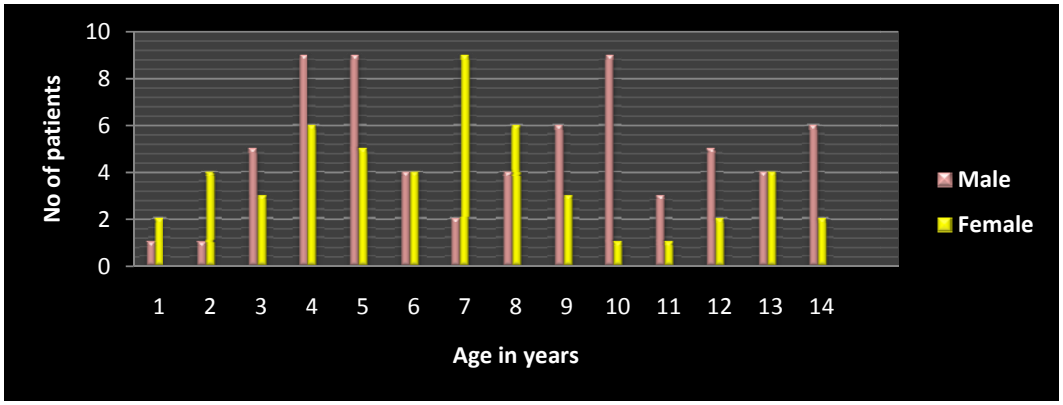
AGE GROUP DISTRIBUTION:

The study was carried out in children affected by nephrotic syndrome and so the patient's age ranged from 1 to 14 years. Majority of cases of the study patient's fall between the age group of 4 to 10 years.

TABLE NO: 2 AGE GROUP DISTRIBUTION

Age in Years	Male	Female	Total
1	1	2	3
2	1	4	5
3	5	3	8
4	9	6	15
5	9	5	14
6	4	4	8
7	2	9	11
8	4	6	10
9	6	3	9
10	9	1	10
11	3	1	4
12	5	2	7
13	4	4	8
14	6	2	8
Total & Percentage	**68 (57%)**	**52 (43%)**	**120 (100%)**

FIGURE NO: 3 AGE GROUP DISTRIBUTION



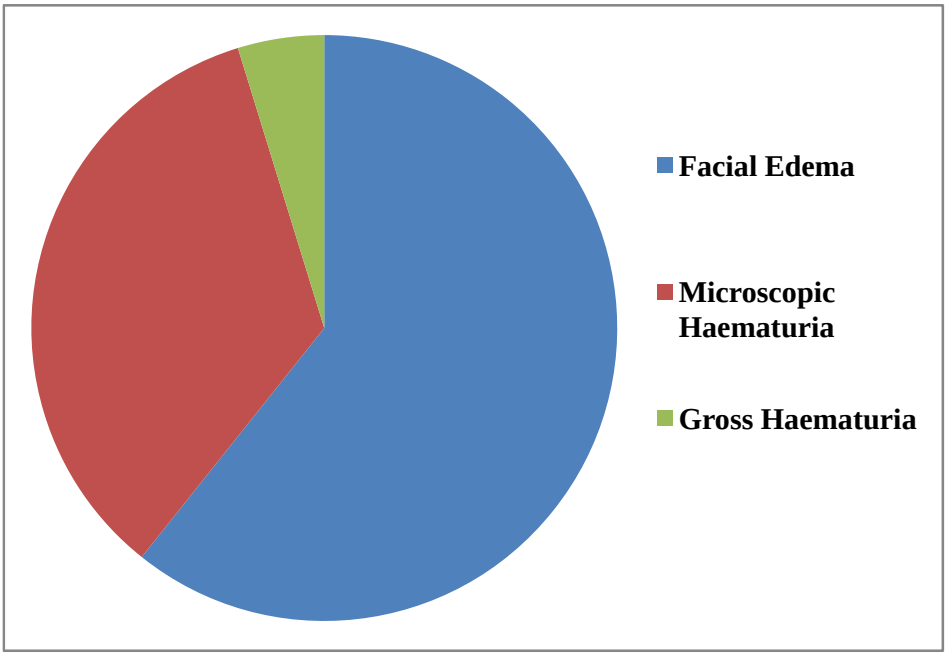
CONDITIONS ASSOCIATED WITH NEPHROTIC SYNDROME

The various conditions associated with nephrotic syndrome were analysed among the patients as follows.

TABLE NO: 3 CONDITIONS ASSOCIATED WITH NEPHROTIC SYNDROME

S.no	Condition	No of patients	Percentage
1	Facial Edema	102	85%
2	Microscopic Haematuria	58	48%
3	Gross Haematuria	8	7%

FIGURE NO: 4CONDITIONS ASSOCIATED WITH NEPHROTIC SYNDROME



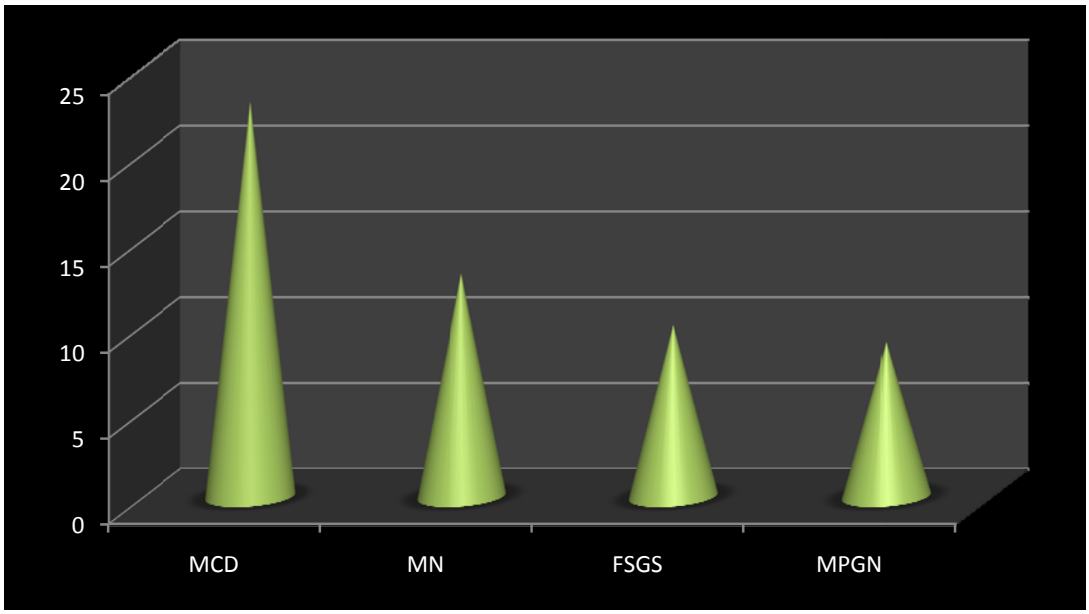
HISTOPATHOLOGICAL DISTRIBUTIONS OF DIFFERENT SUBTYPES OF NEPHROTIC SYNDROME

Nearly 55 children underwent renal biopsy, from which the various sub types of nephrotic syndrome were analysed among the patients and listed below.

TABLE NO: 4 HISTOPATHOLOGICAL DISTRIBUTIONS OF DIFFERENT SUBTYPES OF NEPHROTIC SYNDROME

S.no	Sub Type	No of patients	Percentage
1	Minimal Change Disease (MCD)	23	42%
2	Membranous Nephropathy (MN)	13	24%
3	Focal Segmental Glomerulosclerosis (FSGS)	10	18%
4	Membranoproliferative Glomerulonephritis (MPGN)	9	16%

FIGURE NO: 5HISTOPATHOLOGICAL DISTRIBUTIONS OF DIFFERENT SUBTYPES OF NEPHROTIC SYNDROME



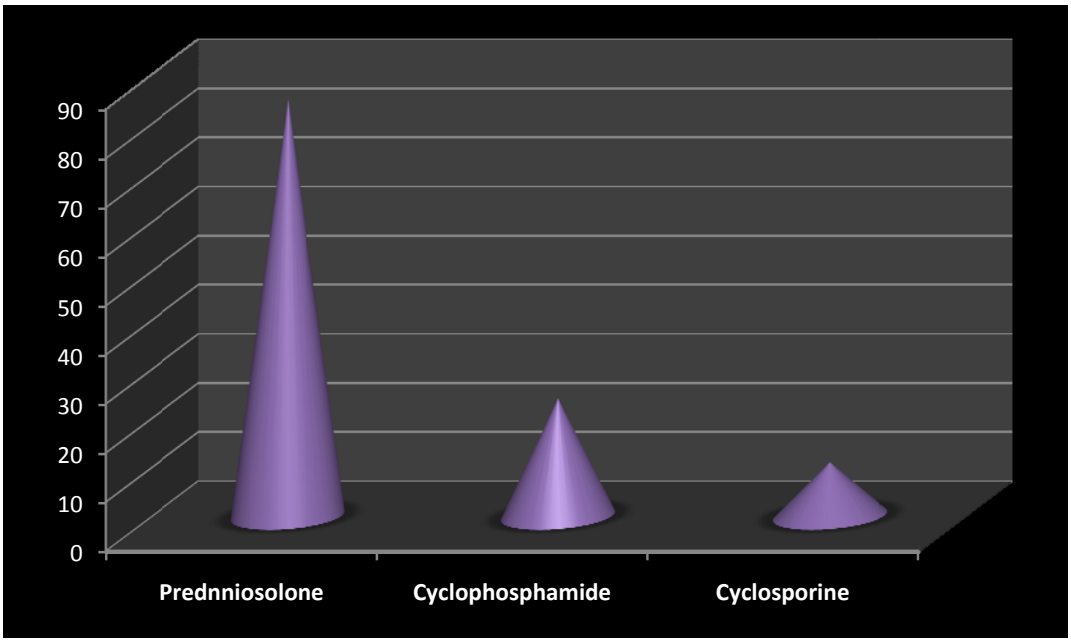
TREATMENT MODALITIES

Among 120 children 85 patients were steroid sensitive and 35 patients were steroid resistant. The steroid sensitive patients 85 (71%) were treated with Prednisolone. In a total of 35 (29%) steroid resistant patients 24 (20%) were treated with cyclophosphamide and 11 (9%) were treated with cyclosporine.

TABLE NO: 5 TREATMENT MODALITIES

Treatment Modality	Steroid Sensitive	Steroid Resistant	
	Prednisolone	Cyclophosphamide	Cyclosporine
No of patients	85	24	11
Percentage	71%	20%	9%

FIGURE NO: 6 TREATMENT MODALITIES



ELEVATIONS IN CLINICAL PARAMETERS:

By monitoring the patient's laboratory data, it is possible to detect the etiology of the disease and as well as the drug response pattern in childhood nephrotic syndrome. The various clinical parameters which were analysed are listed below along with their normal values.

TABLE NO: 6 CLINICAL PARAMETERS

S.no	Parameter	Normal Value
1	Haemoglobin	12.9 to 19.6 g/dl
2	ESR	Upto 20 mm/1 hr
3	Protein / Creatinine Ratio	2 - 3 mg/mg
4	Blood Glucose	80 to 140 mg/dl
5	Plasma Urea	15 to 40 mg/dl
6	Plasma Creatinine	0.4 to 1.4 mg/dl
7	Plasma Cholesterol	110 to 200 mg/dl
8	Plasma Total Protein	6.5 to 8.1 g/dl
9	Plasma Albumin	3.5 to 5 g/dl
10	Plasma Electrolytes	
A	Sodium	135 to 145 mEq/L
B	Potassium	3.5 to 5.1 mEq/L
C	Chloride	98 to 107 mEq/L
D	Bicarbonate	18 to 28 mEq/L

TABLE: 7 CHANGES IN HAEMOGLOBIN CONCENTRATION

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	12.46	13.02	12.15	12.86	11.69	12.95
SEM	0.17	0.10	0.33	0.22	0.60	0.32
SD	1.62	1.04	1.65	1.12	2.08	1.07
P Value	0.0087***		0.0872^{NS}		0.0808^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

^{NS} – P value statistically not significant

FIGURE: 7CHANGES IN HAEMOGLOBIN CONCENTRATION

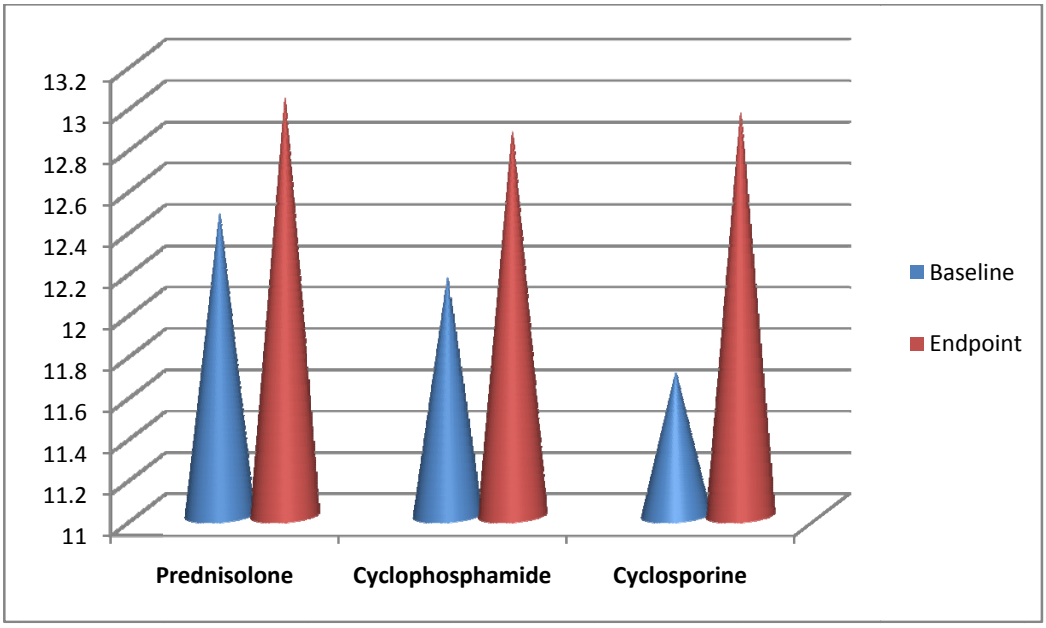


TABLE: 8 CHANGES IN ERYTHROCYTE SEDIMENTATION RATE

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	49.28	27.36	53.25	27	53.45	30.54
SEM	2.43	1.01	5.09	1.87	6.82	2.59
SD	22.47	9.26	24.96	9.16	22.62	8.60
P Value	<0.0001***		<0.0001***		0.0052***	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

FIGURE: 8CHANGES IN ERYHTROCYTE SEDIMENTATION RATE

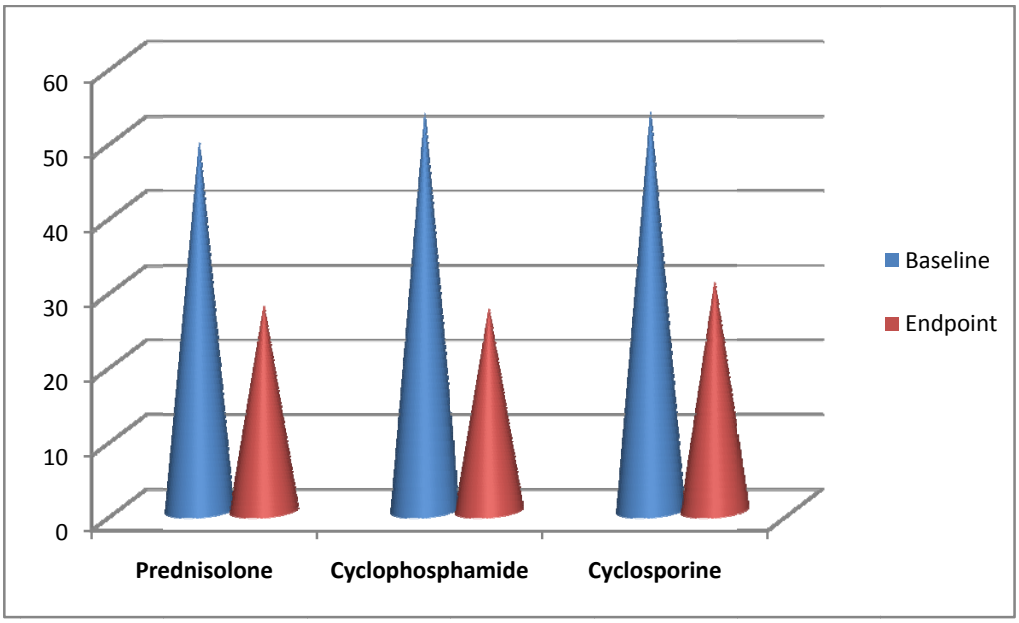


TABLE: 9 CHANGES IN URINE PROTEIN / CREATININE RATIO

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	9.75	7.12	13.22	8.17	24.39	9.33
SEM	0.58	0.31	1.59	0.66	0.82	0.84
SD	5.37	2.86	7.79	3.27	25.94	2.78
P Value	<0.0001***		0.0053**		0.0701^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

** - P value statistically very significant

^{NS} – P value statistically not significant

FIGURE: 9CHANGES IN URINE PROTEIN / CREATININE RATIO

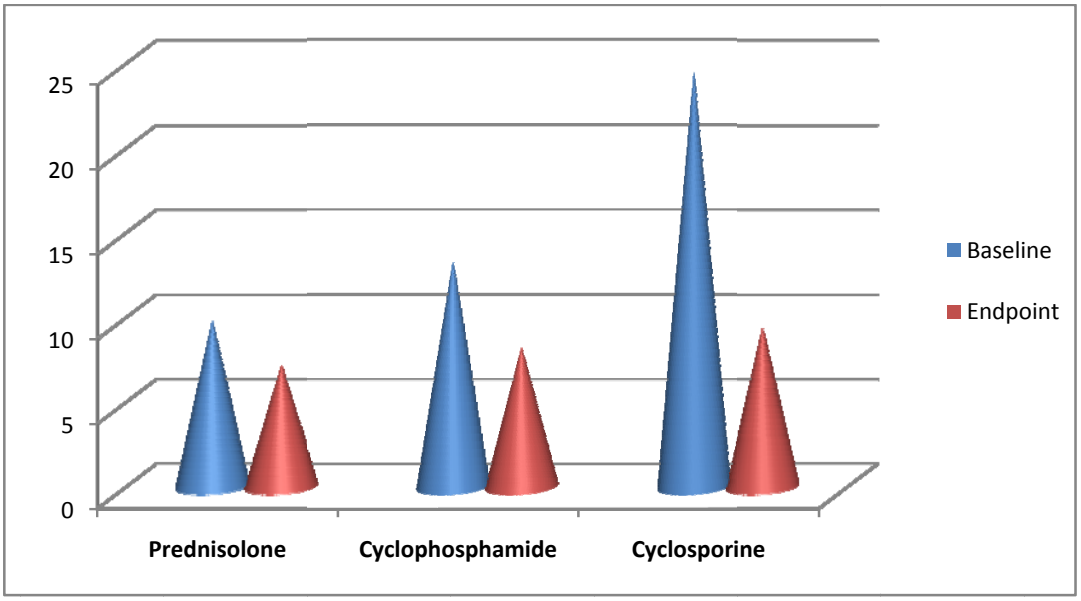


TABLE: 10 CHANGES IN BLOOD GLUCOSE

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	98.52	102.26	100.08	102.62	108	109.72
SEM	1.75	1.48	3.42	2.62	4.95	3.94
SD	16.21	13.68	16.76	12.85	16.42	13.08
P Value	<0.0001***		0.5585^{NS}		0.7878^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

^{NS} – P value statistically not significant

FIGURE: 10CHANGES IN BLOOD GLUCOSE

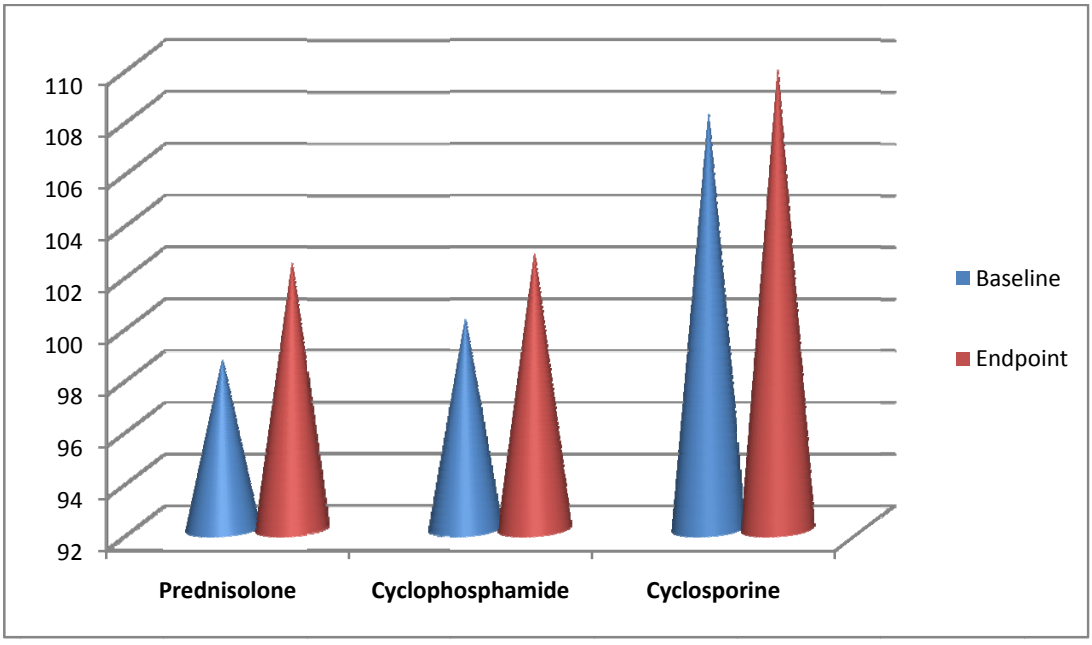


TABLE: 11 CHANGES IN PLASMA UREA

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	50.46	40.61	60.66	43.95	76.18	54.54
SEM	2.31	1.20	6.37	2.34	10.48	4.47
SD	21.32	11.10	31.24	11.47	34.78	14.85
P Value	<0.0001***		0.0178^{NS}		0.0724^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

^{NS} – P value statistically not significant

FIGURE: 11CHANGES IN PLASMA UREA

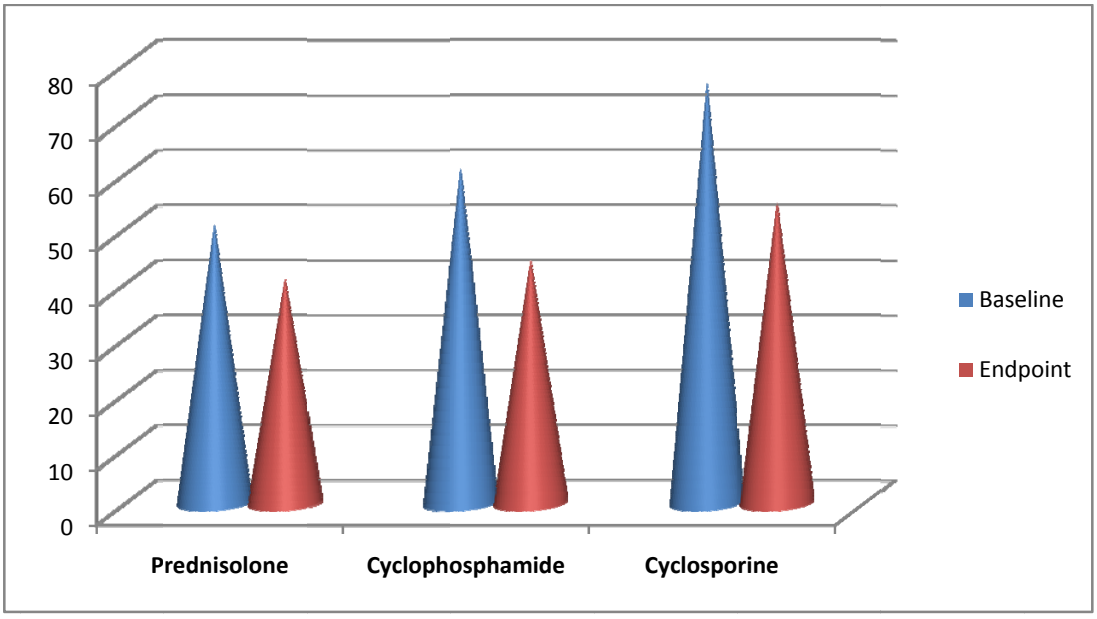


TABLE: 12 CHANGES IN PLASMA CREATININE

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	1.28	1.04	1.55	1.13.	1.18	1
SEM	0.09	0.07	0.15	0.10	0.05	0.04
SD	0.89	0.63	0.76	0.53	0.16	0.14
P Value	<0.0001***		0.0357*		0.0136*	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

* - P value statistically significant

FIGURE: 12CHANGES IN PLASMA CREATININE

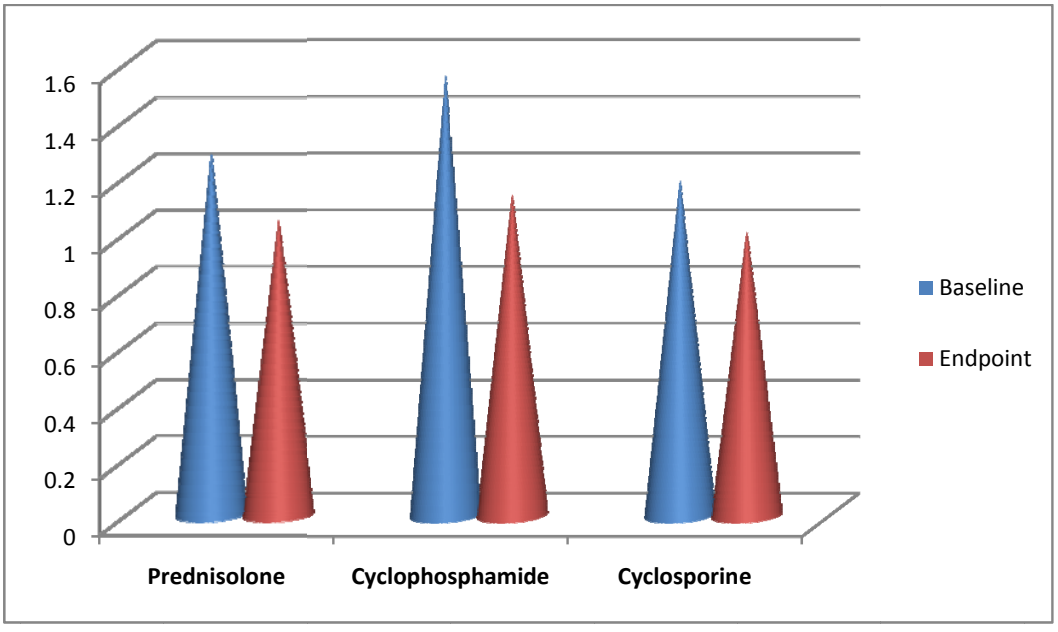


TABLE: 13 CHANGES IN PLASMA CHOLESTEROL

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	405.07	333.96	410.62	340.33	536.54	415.54
SEM	11.48	9.72	24.46	19.38	61.43	35.37
SD	105.92	89.68	119.86	94.96	203.76	117.34
P Value	<0.0001***		0.0291*		0.1033^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

* - P value statistically significant

^{NS} – P value statistically not significant

FIGURE: 13CHANGES IN PLASMA CHOLESTEROL

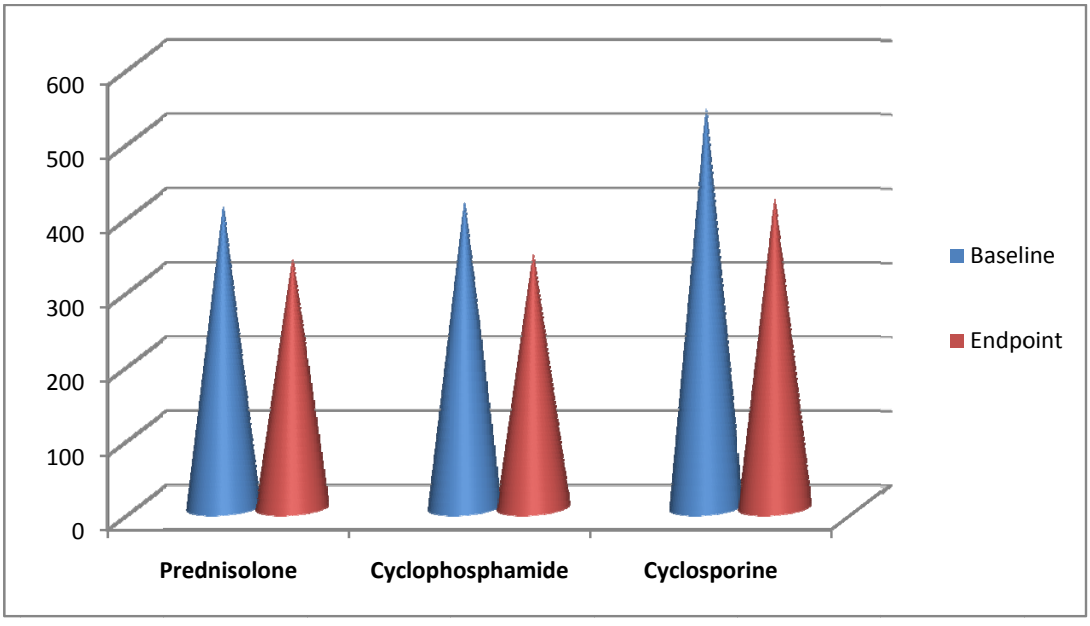


TABLE: 14 CHANGES IN PLASMA TOTAL PROTEIN

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	4.7	5.26	4.89	5.34	4.46	4.99
SEM	0.06	0.07	0.12	0.11	0.24	0.23
SD	0.58	0.56	0.59	0.54	0.82	0.78
P Value	<0.0001***		0.0088**		0.1395^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

** - P value statistically very significant

^{NS} – P value statistically not significant

FIGURE: 14CHANGES IN PLASMA TOTAL PROTEIN

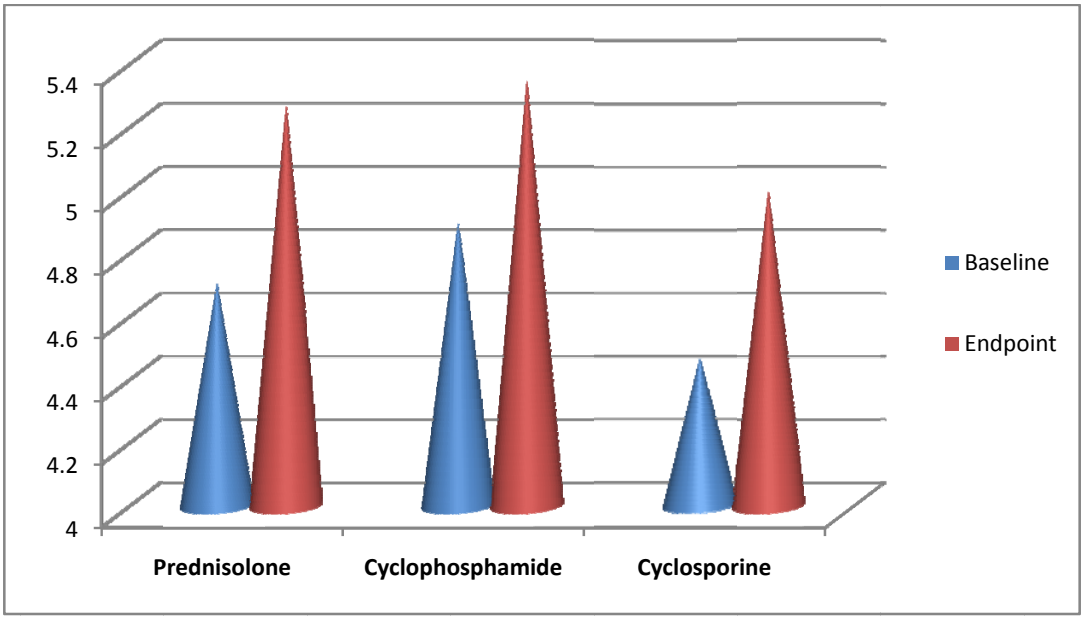


TABLE: 15 CHANGES IN PLASMA ALBUMIN

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	2.03	2.57	1.92	2.46	1.66	2.33
SEM	0.07	0.06	0.12	0.13	0.13	0.17
SD	0.64	0.62	0.60	0.64	0.43	0.56
P Value	<0.0001***		0.0043**		0.0056**	

Values are expressed as mean, standard error mean and standard deviation.

*** - P value statistically extremely significant

** - P value statistically very significant

FIGURE: 15CHANGES IN PLASMA ALBUMIN

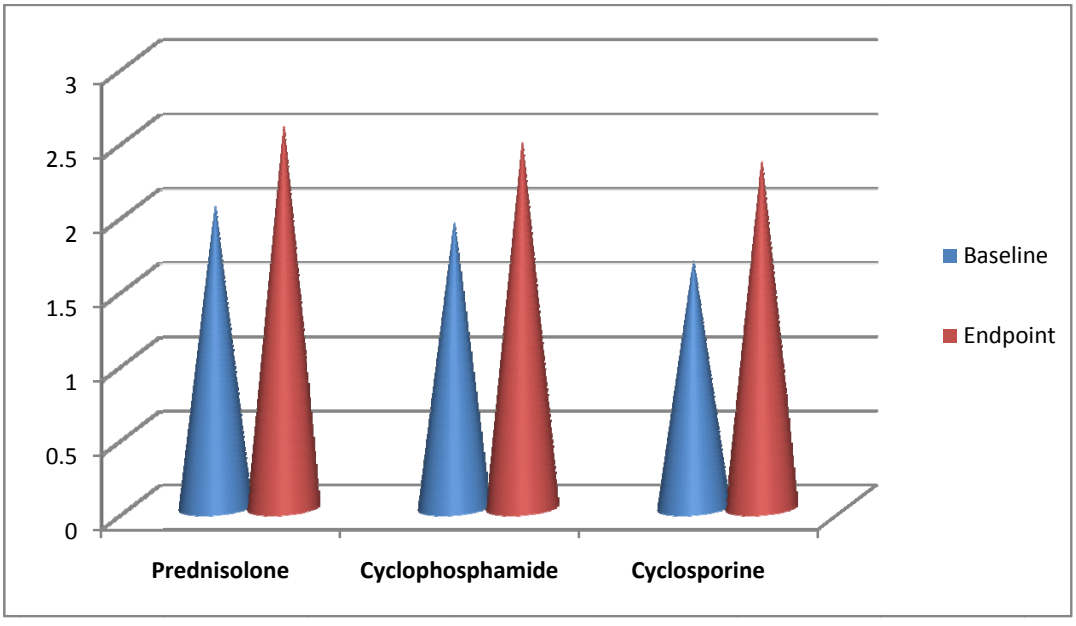


TABLE: 16 CHANGES IN PLASMA ELECTROLYTE - SODIUM

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	134.65	136.09	136.41	137.58	134.81	136.54
SEM	0.44	0.35	0.61	0.55	1.07	0.90
SD	4.11	3.21	3.03	2.73	3.57	3.01
P Value	0.0121**		0.1684^{NS}		0.2345^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

** - P value statistically very significant

^{NS} – P value statistically not significant

FIGURE: 16CHANGES IN PLASMA ELECTROLYTE – SODIUM

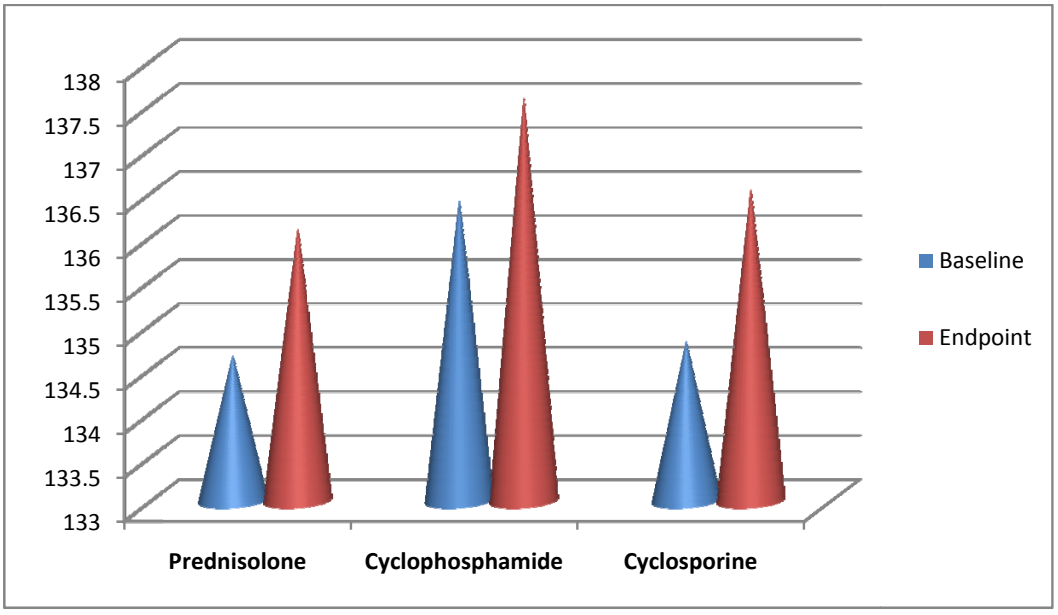


TABLE: 17 CHANGES IN PLASMA ELECTROLYTE – POTASSIUM

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	3.86	4.06	3.92	4.10	4.29	4.52
SEM	0.06	0.05	0.12	0.11	0.22	0.19
SD	0.54	0.49	0.57	0.55	0.75	0.63
P Value	0.0145**		0.2643^{NS}		0.4366^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

** - P value statistically very significant

^{NS} – P value statistically not significant

FIGURE: 17CHANGES IN PLASMA ELECTROLYTE – POTASSIUM

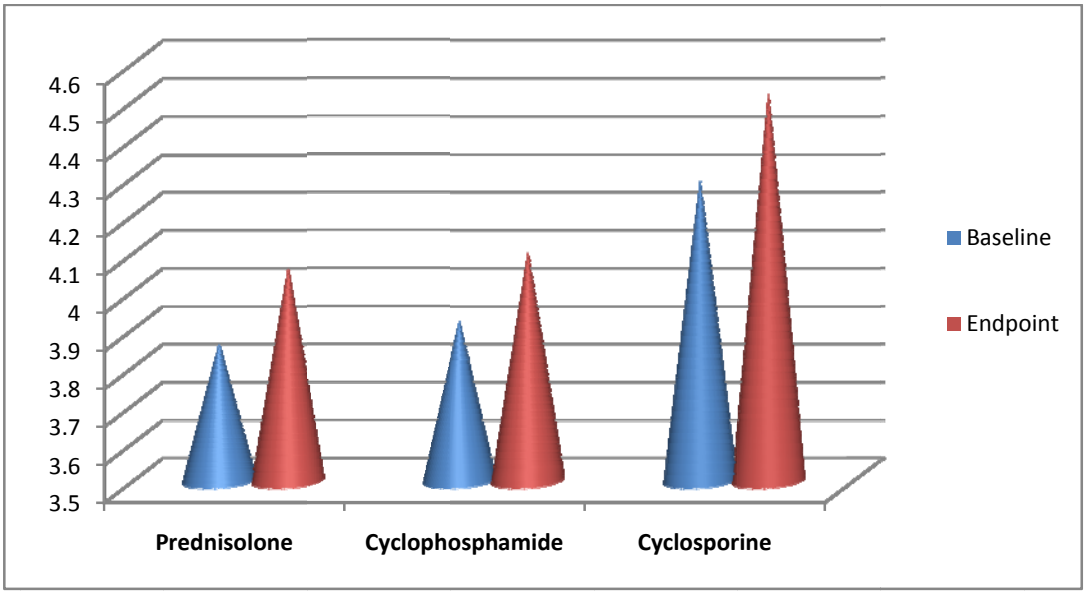


TABLE: 18 CHANGES IN PLASMA ELECTROLYTE – CHLORIDE

Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	97.90	99.07	97.25	98.83	96.63	97.82
SEM	0.42	0.33	0.72	0.63	1.44	0.94
SD	3.91	3.04	3.55	3.13	4.80	3.12
P Value	0.0318*		0.1083^{NS}		0.5017^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

* - P value statistically significant

^{NS} – P value statistically not significant

FIGURE: 18CHANGES IN PLASMA ELECTROLYTE – CHLORIDE

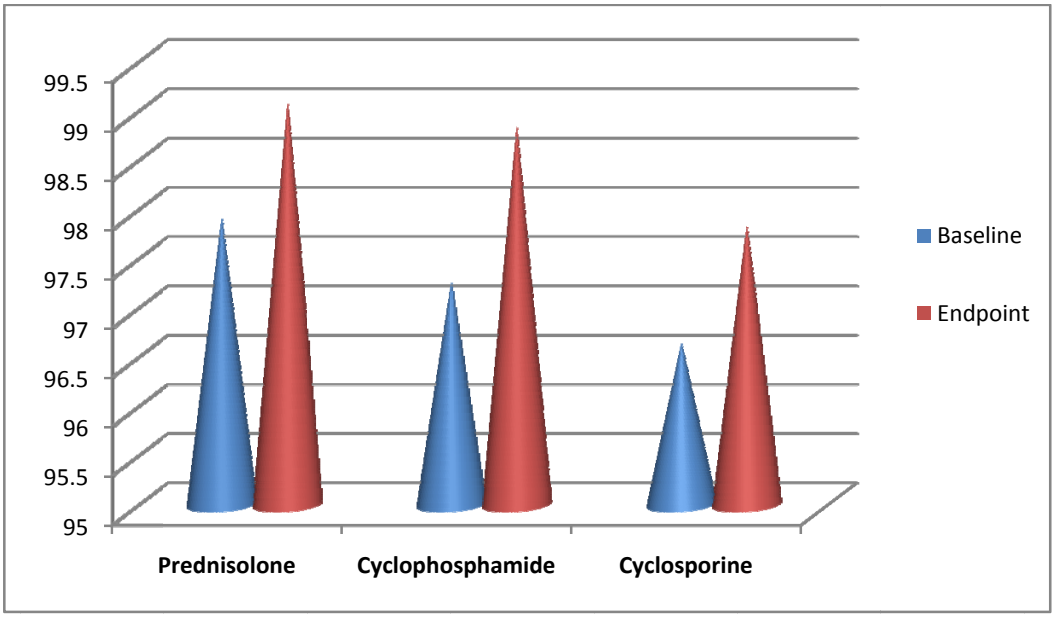


TABLE: 19 CHANGES IN PLASMA ELECTROLYTE – BICARBONATE

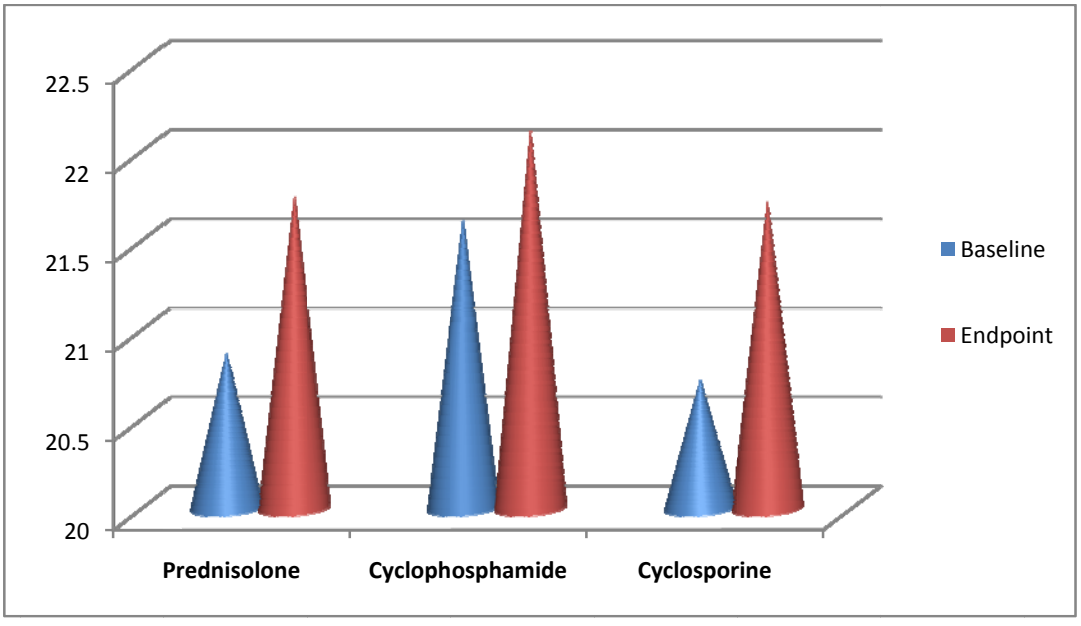
Values	Steroid Sensitive		Steroid Resistant			
	Prednisolone		Cyclophosphamide		Cyclosporine	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean	20.87	21.75	21.62	22.12	20.72	21.72
SEM	0.28	0.22	0.71	0.49	0.61	0.54
SD	2.56	2.06	3.49	2.43	2.05	1.79
P Value	0.0145*		0.5685^{NS}		0.2381^{NS}	

Values are expressed as mean, standard error mean and standard deviation.

* - P value statistically significant

^{NS} – P value statistically not significant

FIGURE: 19CHANGES IN PLASMA ELECTROLYTE – BICARBONATE



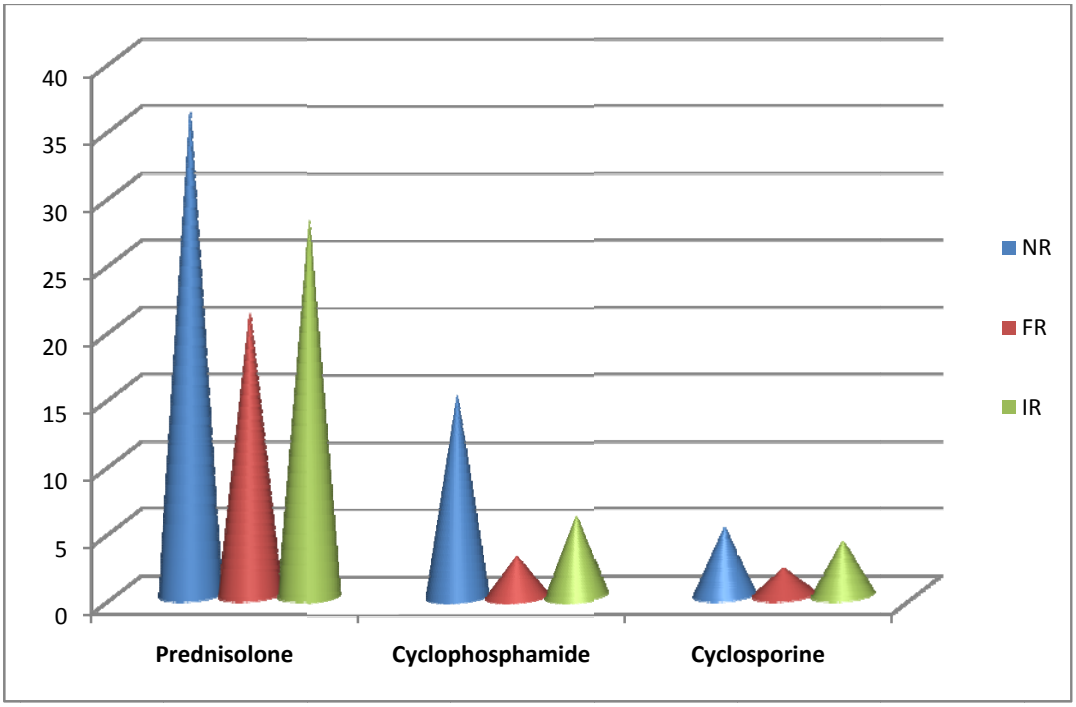
RELAPSE PATTERN

Relapse is the occurrence of 3+–4+ proteinuria plus edema. Here the relapse pattern is divided as non-relapsers, frequent relapsers and infrequent relapsers. The relapse pattern of patients with different treatment modalities are listed below.

TABLE: 20RELAPSE PATTERN

Relapse pattern	Steroid sensitive	Steroid Resistant		Total & Percentage
	Prednisolone	Cyclophosphamide	Cyclosporine	
Non-Relapsers (NR)	36 (42%)	15(63%)	5(46%)	56(47%)
Frequent Relapsers (FR)	21(25%)	3(12%)	2(18%)	26(22%)
Infrequent Relapsers (IR)	28(33%)	6(25%)	4(36%)	38(31%)

FIGURE: 20 RELAPSE PATTERN



REMISSION PATTERN

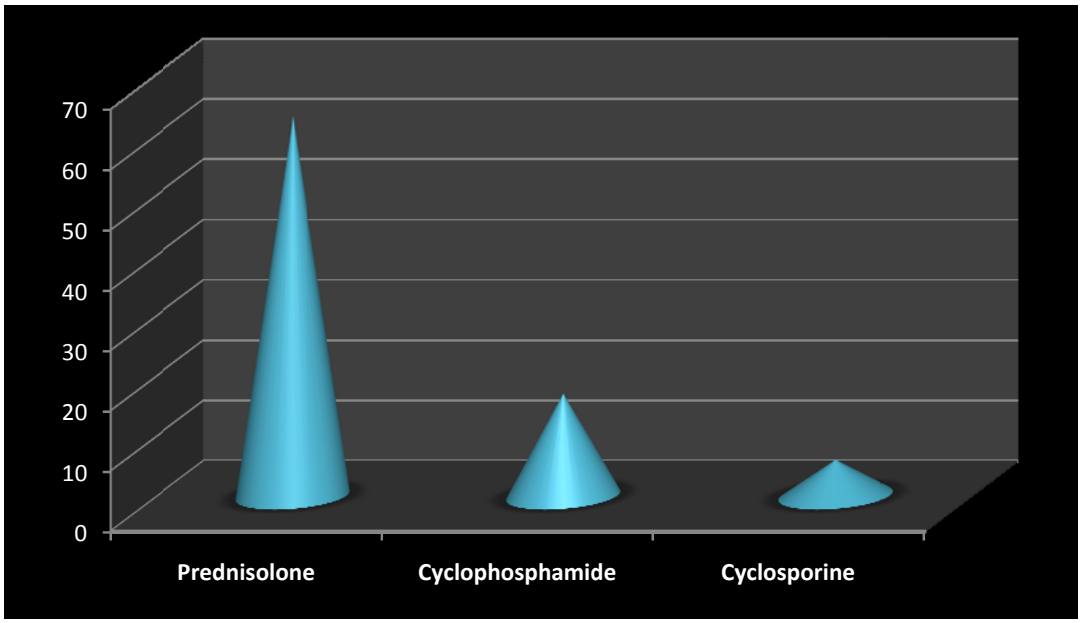
Remission is nothing but urinary protein excretion <4 mg/m²/h; nil or trace by dipstick on spot sample for 3 consecutive days.

Out of 120 patients 86 (72%) achieved good remission with any one of the treatment modalities. Most of the patients who showed good remission experienced at least one recurrence during the follow up period. The remission pattern by different drug modalities is listed below.

TABLE: 21REMISSION PATTERN

Remission	Steroid Sensitive	Steroid Resistance		Total& Percentage
	Prednisolone	Cyclophosphamide	Cyclosporine	
No of patients	63	17	6	86 (72%)

FIGURE: 21 REMISSION PATTERN



DISCUSSION

Patients with nephrotic syndrome loose massive amounts of protein in the urine leading to hypoproteinemia and its result, edema. Hyperlipidemia, hypercholesterolemia, and increased lipiduria are also associated. In this study, we analyzed all children with nephrotic syndrome referred to Meenakshi mission hospital and research center, Madurai.

The study group included 120 children with age up to 14 years. There were 68 (57%) boys and 52 (43%) girls. The mean age of boys was 7.9±0.4 years and those of girls were 6.8±0.5 years. Majority of cases of the study patient's fall between the age group of 4 to 10 years.

The various conditions associated with nephrotic syndrome were analysed among the patients. Facial edema was found in 102 (58%), microscopic haematuria in 58 (48%) and gross haematuria in 8 (7%) patients.

Nearly 55 children underwent renal biopsy from which the various sub types of nephrotic syndrome were analysed among the patients. The minimal change disease was the most common pathological finding 23 (42%) patients. The other sub types include Membranous Nephropathy in 13 (24%), Focal Segmental Glomeruloslerosis in 10 (18%) and Membranoproliferative Glomerulonephritis in 9 (16%) cases.

The responsive patterns for the treatment have been studied. Among 120 children 85 (71%) were steroid sensitive and 35 (29%) were steroid resistant. The steroid sensitive patients have been treated with prednisolone. In a total of 35 steroid resistant patients 24 (20%) were treated with cyclophosphamide and 11 (9%) were treated with cyclosporine.

Patients who had no indication for renal biopsy were treated with prednisolone 60 mg/m^2/day for 4–6 weeks followed by prednisolone 40 mg/m^2 on alternate days for a further 4 weeks. The prednisolone dose was then tapered and discontinued over

the next 2–3 months. Steroid resistant's and frequent relapsers underwent treatment with other alternative agents including cyclophosphamide (2–3 mg/kg/day for 8–12 months) and cyclosporine (3–6 mg/kg/day).

Various clinical parameters such as haemoglobin, erythrocyte sedimentation rate, blood glucose, urinalysis and microscopy, 24-hour urinary protein excretion, creatinine clearance, plasma total protein, plasma albumin, plasma cholesterol, serum electrolytes, serum urea and creatinine levels were studied to find out the effectiveness of the treatment pattern.

Among the steroid sensitive group who were treated with prednisolone showed significant change in the parameters. The values were expressed as Mean ± SEM. There was increase in values for haemoglobin (12.46±0.17 to 13.02±0.10), plasma total protein (4.7±0.06 to 5.26±0.07) and plasma albumin (2.03±0.07 to 2.57±0.06) after treatment. Urine protein/creatinine ratio (9.75±0.58 to 7.12±0.31), erythrocyte sedimentation rate (49.28±2.43 to 27.36±1.04), plasma urea (50.46±2.31 to 40.61±1.20), plasma creatinine (1.28±0.09 to 1.04±0.06) and plasma cholesterol (405.07±11.48 to 333.96±9.72) decreased significantly after treatment. The P value was < 0.05 for all the above parameters showing extreme significance.

The steroid resistant nephrotic syndrome patients were treated with cyclophosphamide and cycloserine. For patients treated with cyclophosphamide the changes in the values of various clinical parameters are as follows: haemoglobin (12.15±0.33 to 12.86±0.22), plasma total protein (4.89±0.12 to 5.34±0.11), plasma albumin (1.92±0.12 to 2.46±0.13), erythrocyte sedimentation rate (53.25±5.09 to 27±1.87), urine protein/creatinine ratio (13.22±1.59 to 8.17±0.66), plasma urea (60.66±6.37 to 43.95±2.34), plasma creatinine (1.55±0.15 to 1.13±0.10) and plasma cholesterol (410.62±24.46 to 340.33±19.38).

Among the patients treated with cyclosporine the changes in the values of various clinical parameters are haemoglobin (11.69±0.60 to 12.95±0.32), plasma total protein (4.46±0.24 to 4.99±0.23), plasma albumin (1.66±0.13 to 2.33±0.17), erythrocyte sedimentation rate (53.45±6.82 to 30.542.59), urine protein/creatinine ratio (24.39±0.82 to 9.33±0.84), plasma urea (76.18±10.48 to 54.54±4.47), plasma

creatinine (1.18±0.05 to 1±0.04) and plasma cholesterol (536.54±61.43 to 415.54±35.37).

The P value was < 0.05 (extremely significant) for erythrocyte sedimentation rate, plasma urea, plasma creatinine, plasma total protein and plasma albumin in both cyclophosphamide and cycloserine treated patients. There was only slight change in the other parameters which were not statistically significant (P > 0.05).

There was slight increase in the serum electrolytes sodium, potassium, chloride and bicarbonate in all the above mentioned treatment modalities, showing a good significant value.

Out of 85 patients who were steroid sensitive 36 (42%) were non – relapsers, 21 (25%) were frequent relapsers and 28 (33%) were infrequent relapsers.

Out of 24 patients who were treated with cyclophosphamide 15 (63%) were non – relapsers, 3 (12%) were frequent relapsers and 6 (25%) were infrequent relapsers.

Out of 11 patients who were treated with cyclosporine 5 (46%) were non – relapsers, 2 (18%) were frequent relapsers and 4 (36%) were infrequent relapsers.

In a total of 120 patients 86 (72%) achieved good remission with any one of the treatment modalities. Most of the patients who showed good remission experienced at least one recurrence during the follow up period. The remission pattern by different drug modalities are prednisolone 63 patients, cyclophosphamide 17 patients and cyclosporine 6 patients.

CONCLUSION

Gender and age distribution, histological features, steroid response pattern, and outcome of nephrotic syndrome were successfully studied. The cure rate was very significant in steroid sensitive nephrotic syndrome patients (SSNS) who were treated with prednisolone.

The study shows that both the treatments cyclophosphamide and cyclosporine are effective and well tolerated in the steroid resistant nephrotic syndrome patients (SRNS). The rate of subsequent relapses and remission seems to be lower in patients who received cyclophosphamide than in those treated with prednisolone and cyclosporine.

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